Company-Organized Symposium

1-CS1-1

Consistency of the pharmacodynamic index required for the decisions in drug discovery and drug development moving from the preclinical to the clinical studies

Masaharu Shiotani[1]

[1]Sohyaku, Innovative Research Division, Mitsubishi Tanabe Pharma Corp.

Relationship between pharmacokinetics (PK) of candidate substances and pharmacodynamic changes caused by candidate substances, i.e., PK/PD is requested to maintain consistency among different R&D stages from in vitro to in vivo or from nonclinical to clinical. It is essential to anticipate clinical efficacy and to verify its outcome in clinical trials. However, there are few data available for modeling and simulation when selecting molecular targets in the early stages of drug discovery and screening candidate substances from various compounds, and it is extremely challenging to quantitatively consider the extrapolation to the clinical. Furthermore, efficacy assessments often take into account species differences in targets and limited suitability with the clinical manifestations of animal models, which often require individualized assessment depending on the target molecule or disease state.

In this topic, we will discuss the improvement of the success rate of drug discovery and development from the viewpoint of efficacy through the introduction of some cases for our type 2 diabetes drugs from the discovery to the post-launch stage.

Company-Organized Symposium

1-CS1-2

Development of Precision Medicine Utilizing Biomarker That Identifies Eligible Patients

Yasuo Ochi[1]

[1]Drug Safety Research and Development, Pfizer R&D Japan

Predictive biomarkers being used as companion diagnostic agents will help to avoid critical failures of drug treatment due to a lack of efficacy. Therefore, the predictive biomarkers can reduce the number of patients needed to demonstrate the efficacy in clinical trials by enriching the populations with biomarker-positive patients. In addition, this allows avoiding adverse effects by unnecessary treatment. The presence or absence of the target molecule-related gene expression can be such a biomarker. As an example, aberrant activation of anaplastic lymphoma kinase (ALK) after being fused with echinoderm microtubule-associated protein-like 4 (EML4) shows oncogenic potential and the underlying genetic rearrangement is the oncogene in a small subset of non-small cell lung cancer (NSCLC). ALK inhibitors and companion diagnostic agents to detect the fusion gene have been developed simultaneously and approved for ALK fusion gene-positive NSCLC. This represented a landmark in oncology drug development and a significant step toward precision medicine. In this presentation, the current situation of predictive biomarker-driven drug development will be discussed.

Company-Organized Symposium

1-CS1-3

Translational science as a key for improving success rate of drug development

Jun Tanaka[1]

[1]Biomarker Department, Group II / DAIICHI SANKYO CO.,LTD.

Our target diseases with high unmet needs are getting more and more complicated and heterogeneous. Accordingly, to predict clinical efficacy of drugs in the preclinical stages, we should avoid relying too much on phenotypically resemble animal models, but seek more mechanistic, human-predictive models. Thanks to accumulation of publicly-available biomedical information, understanding of pathophysiological mechanisms for both patients and disease animal models can be improved. Systems Biology / Pharmacology are practical Translational Science tools to handle such large-scale biomedical data. For instance, Systems Biology analysis with patient transcriptome data can decipher disease mechanisms, and support creating competitive drug concepts. Quantitative systems pharmacology (QSP) modeling & simulation can provide us with rational clinical efficacy prediction based on the currently-best knowledge. Through the model-based approach, we can continuously and rationally decrease the uncertainties, and identify key research questions to be addressed by both preclinical and clinical researches. I will show some examples for applications of translational science tools to address some research questions in the drug development researches.

Company-Organized Symposium

1-CS1-4
Genetics & Pathophysiology-based Drug Discovery in Psychiatry

Mitsuyuki Matsumoto[1]

[1]Executive Director, Head, Unit 2, Candidate Discovery Science Labs. Drug Discovery Research, Astellas Pharma Inc..

The largely unknown etiology and pathophysiology of psychiatric disorders has significantly hampered effective drug discovery and development; to wit, nearly all first-generation antipsychotics and mood stabilizers have been discovered under serendipitous circumstances. However, recent advances in genetics and pathological technologies have provided new avenues into investigating and connecting genetic components in the etiology of psychiatric disorders with pathophysiological changes in the patient's brain. With this newfound synergy, we are now able to commence truly innovative drug discovery based on strong scientific rationale.

Our approach is to pinpoint common biological pathways disturbed in both psychiatric patients and genetically-engineered animal models (targeting both individual genes and CNVs discovered in patients) and use these commonalities to generate testable working hypotheses. We have obtained patient datasets via participation in the Lieber Institute for Brain Development's (LIBD) Pharma RNA-Seq Consortium, BrainSEQ^{TM}, a precompetitive research collaboration aimed at completing RNA sequencing of up to 800 brain samples from DLPFC and hippocampus. This approach facilitates streamlined, comprehensive drug target selection where candidate compounds are evaluated using behavioral testing and pathophysiological measures, with the eventual goal of reversing the disturbed pathways in gene-manipulated animal models and, ultimately, human patients. Our objective is to achieve precision medicine in psychiatry. In doing this, we aim to tackle emerging problems, including disease- and patient-specific biomarkers used for diagnosis and stratification.

1-ES1-1

Vertical and horizontal curriculum integration of pharmacology: Overview

Shoshiro Okada[1]

[1]Dept. Pharmacol., Sch. Med., Aichi Med. Univ.

Lately, integrating liberal arts and basic medicine is being discussed in various fields. The discussion stresses the shift from the teaching method that attempts to stuff students with knowledge, as many of us have hitherto done, to the one that teaches students important principles repeatedly and encourages them to learn voluntarily, so-called active learning. The shift from passive learning to active learning directs us to a new medical education where students are required not just to acquire knowledge (I know xxx) but also to perform based on the knowledge (I can do xxx). In addition, medical schools are to follow the model core curriculum, which was revised in 2017. Taking into consideration the changes in international public health and medical systems, it notes that the medical school curriculum should train students to have practical clinical abilities with which they respond to citizens' needs for ethics, medical safety, team medical care, regional inclusive care system, healthy longevity society, etc. While medical schools are expected to make such a transformation from the traditional approach, they need to meet the international certification standards, which require students to engage in clinical practice for at least 1/3 of their six-year medical education. It is not an exaggeration to say that it is impossible for us to continue traditional lecture-style classes covering the same contents of liberal arts and basic medicine. Instead, we should actively integrate the curriculum.

Pharmacology is a broad science (1) representing a comprehensive summary of anatomy, physiology, and biochemistry from a viewpoint of the action mechanism of drugs, on one hand, and (2) relating various clinical practices from a viewpoint of therapeutic drugs for different diseases in clinical medicine, on the other. Benefiting from the contents of (1) and (2), it can and should integrate well with other fields of study in the curriculum.

1-ES1-2

Integration of medical curriculum- Physiology, Pharmacology and Clinical Medicine

Noriyuki Koibuchi[1]

[1]Dept. Integrative Physiol. Gunma Univ. Grad. Sch. Med.

Traditionally, discipline-based education is the most commonly applied educational method for undergraduate education. However, problem-solving in real-life settings requires skills to integrate various knowledge. To educate such skill to medical students, integrative curriculum that includes various disciplines, such as anatomy, physiology, biochemistry, pharmacology and clinical medicine, needs to be constructed. For such purpose, we use team-based learning (TBL) using clinical cases. Unlike problem-based learning (PBL), in which students should find problems by themselves, questions for TBL are prepared by moderators (teachers). TBL can be given after a set of lecture corses, such as endocrine physiology. During the TBL class, after clinical case presentation, teachers give tasks to students, (e.g., "Describe abnormal symptoms and explain why", "Why doctor prescribed this drug?"). Students should discuss within the team (4〜6 students/team) to answer such questions by integrating their knowledge obtained through lectures. Then teacher randomly ask students and evaluate as a team so that all students within a team should share the common knowledge and ideas. Using this strategy, various disciplines can be integrated. Students can learn how to integrate their knowledge fo solve real-life setting questions. Furthermore, students can understand the importance to learn basic medicine through such experience.

1-ES1-3

Integrated curriculum of pharmacology and clinical pharmacology for medical schools: Optimistic perspectives

Shinichiro Ueda[1]

[1]Department of Clinical Pharmacology & Therapeutics, University of the Ryukyus Graduate School of Medicine

Since prevention of prescription error with understanding drug actions should be one of pragmatic outcomes for all medical students, curriculum of pharmacology and clinical pharmacology at medical school should be integrated to achieve this purpose. There are, however, very few clinical pharmacologists in Japan. Drugs are prescribed by nearly all doctors, most would see themselves as practicing clinical pharmacology & therapeutics every day. Clinical pharmacology, even if with strong clinical background, has looked weak as a specialty without an organ or a disease. Clinical pharmacologists/pharmacologist used to have a close relationship with research into, and management of chronic common diseases such as cardiovascular diseases, which has increasingly devoted to specialists or primary care. More importantly, the shift from pharmacology(theory)-based medicine to evidence based medicine after the CAST trial has effect curriculum of medical schools.

We should not, however, be too pessimistic. Current problem regarding drug therapy such as polypharmacy and potential inappropriate prescription may be handled by clinical pharmacologists rather than specialists. Development of functional biomarkers based on pharmacological action to describe patients who will benefit from new drugs may lead to precision medicine.

1-ES1-4

Horizontal relay lecture among anatomy, pathology and pharmacology: experience and problems

Naohiko Anzai[1], Atsushi Yamaguchi[2], Yuzuru Ikehara[3]

[1]Dept. Pharmacol., Grad. Sch. Med., Chiba Univ., [2]Dept. Func. Anat., Grad. Sch. Med., Chiba Univ., [3]Dept. Oncol. Pathol., Grad. Sch. Med., Chiba Univ.

Currently, medical schools in Japan are under pressure to reform the curriculum to respond to field-specific certification, which is the quality assurance system of medical education. Among the criteria required by field certification, the curriculum of many medical schools in Japan is one of the points to overcome is curriculum integration. "Integration" here means "to relate learning matters taught in different academic systems or departments to each other, unite and organize". There are two types of "integration" required for the curriculum: "horizontal integration" and "vertical integration". "Horizontal integration" means that by integrating individual scientific systems among basic medicine or among clinical medicine, "Vertical integration" refers to the longitudinal integration of basic medicine and clinical medicine.

Looking at the curriculum integration of nine universities that have published external evaluation results out of universities that have undergone external trial by FY 2015 according to JACME (The Japan Accreditation Council for Medical Education and Evaluation Organization) standards. Although both the horizontal integration and the vertical integration have been partially accomplished at many universities, there are not many universities that have achieved complete integration, which is said to be a future task.

Here, I report on the experience that I gave a lecture on digestive system relays by three departments of anatomy, pathology, pharmacology, to the third grade of medical school.

1-ES1-5

Horizontal integration of Pharmacology, Anatomy, Physiology and Biochemistry by common term of “Neuroscience”

Schuichi Koizumi[1]

[1]Dept Neuropharmacol, Interdisciplinary Grad Sch Med, Univ Yamanashi

We often receive suggestion from authorities on the importance of horizontal or vertical integration of lectures. The integration is important in a sense but must not be a purpose. Instead, we need proper reasons for the integration, i.e. benefit for both students and teachers. To make a new subject "Neuroscience" is very good reason for the horizontal integration. The progress of neuroscience is remarkable, but we had neither subject named "neuroscience" nor lecture system to teach this systematically. Therefore, we integrated some parts of lecture of anatomy, physiology, biochemistry and pharmacology horizontally for new subject neuroscience. In general, neuroscience course progresses in the order of structure, function, biochemistry and medication treatment, each of which is in charge of 2 anatomy, 2 physiology, 1 biochemistry and 1 pharmacology departments. By prior arrangements, we are trying to avoid duplication or teaching omission. After completing the neuroscience course, we take a questionnaire and continue devising to make better horizontal integration. Our horizontal integration has just started and still has a lot of problems. We would like to share its benefits and problems in this symposium.

1-ES1-6

A vertical integration lecture of biochemistry, pharmacology, and anesthesiology ～The advantage and problems of the lecture～

Toshiiaki Ishizuka[1]

[1]Dept. Pharmacol., National Defense Medical College

For accreditation for medical education by JACME (Japan Accreditation Council for Medical Education), a new curriculum in my school has been started from a few years ago. Many departments adopted new integrated medical lectures. In my department, collaborative studies with many departments such as physiology, biochemistry, anesthesiology, psychiatry, or infectious diseases has been carried out. At the edge of these collaborative studies, several horizontal or vertical integration lectures have been planned (ex. Basic principles and clinical use of antibiotics, neurotransmitters and psychotropic drugs, ect …). In particular, I mention a vertical integration lecture of biochemistry, pharmacology, and anesthesiology. The advantage of the integration lectures is that the students recognize basic medical sciences are valid for medical education. However, a lot of effort is required to succeed the lectures. Advanced discussions with all teachers involved in the lectures are needed to remove overlapping contents. Visual effects using moving pictures about medical activities such as operations, anesthesia, or medical practice can cultivate a better understanding for the pre-CC (clinical clerkship) students.

Joint Symposium

1-JS1-1

Mechanisms underlying the pathogenesis and treatment of neurological disorders: Extrapyramidal motor disorders

Yukihiro Ohno[1], Saki Shimizu[1]

[1]Dept. Pharmacol., Osaka Univ. Pharm. Sci.

Various agents (e.g., prescription drugs, OTC-medications, agricultural chemicals) have a potential to cause neurological disorders including cognitive impairment, movement disorders, convulsions and peripheral neuropathy. Among them, extrapyramidal motor disorders (e.g., parkinsonian symptoms and tremor) are often caused by drugs acting on central nervous system, deteriorating quality of life in many patients. Recent progress in pharmacology/drug safety research revealed detailed mechanisms for the pathogenesis and treatment of drug-induced extrapyramidal side effects (EPS). Although the dopaminergic system dysfunction has long been considered to be the primary cause of parkinsonian symptoms, it is now known that multiple serotonergic (5-HT_{1A}, 5-HT_{2A}, 5-HT_3 and 5-HT_6 receptors), adrenergic (α_{2A} and α_{2C} receptors) or cholinergic (muscarinic) receptors play crucial roles in modulating the EPS induction. In this presentation, we introduce the mechanisms underlying the pathogenesis and treatment of EPS, with a focus on drug-induced parkinsonian symptoms and tremor, and discuss the prediction and management of EPS at clinical settings (e.g., treatment of schizophrenia, mood disorders, Alzheimer's disease) and chemical intoxication.

1-JS1-2

Developmental mechanism of psychiatric disorders: psychobehavioral impairments according to neurodevelopmental abnormalities

Yukihiro Noda[1]

[1]Div. Clin. Sci. Neuropsychopharmacol., Meijo Univ. Fac. & Grad. Sch. Pharm.

Glutamate transporters (GLTs), which regulate glutamatergic transmission are mainly localized on glial cells. Glial disruption results in decreased uptake of glutamate and an elevation in extracellular glutamate levels. Elevated extracellular glutamate may cause cytotoxic damage to neurons and glia. Abnormalities of GLTs cause some neurodevelopmental disorders, such as ADHD and schizophrenia. A recent study found an increased incidence of a rare genetic variant in the human gene encoding glial glutamate and aspartate transporter (GLAST; one of GLT family) in schizophrenia. The loss of GLAST is predicted to cause glutamate excess that provoke glutamate release. In fact, the deficient of GLAST induces some behavioral abnormalities and morphological changes in mice. During the adolescent period, further, mice that had received the combination of neonatal viral infection and adolescent drug abuse exhibits some psychobehavioral abnormalities and increased expression of GLAST. In this symposium, we will present the recent advances of our researches, regarding functional roles of GLAST in neurodevelopment under the physiological and pathological conditions using the mice with varying expression of GLAST.

Joint Symposium

1-JS1-3

Development of a new in vitro neurotoxicity method using iPS cell technology and international trend

Yasunari Kanda[1]

[1]Div Pharmacol, NIHS

The central nervous system is a target organ for environmental toxicants and medicinal drugs. Since the central nervous system is complex and it is difficult to obtain human neuronal cells, establishment of complete neuronal functionality of in vitro cellular models is a great challenge for chemical/drug safety issues. Here we present the framework of iPS cell-based assays regarding neurodevelopmental studies and drug safety assessment toward global standardization. Neurotoxicity can be divided into structural and functional aspects and we have collaborated with OECD developmental neurotoxicity group as well as international consortium HESI (NeuTox subteam) to make new test methods. I would like to show our research activities and discuss future perspectives toward in vitro neurotoxicity method using iPS cell technology.

1-JS1-4

Development of an evaluation assay for drug-induced seizure liability using human iPSC derived neurons

Ikurou Suzuki[1]

[1]Dept. Electronics., Grad. Sch. Eng., Tohoku institute of Tech.

Human induced pluripotent stem cell-derived neurons are promising for use in toxicity evaluations in nonclinical studies. One of the major adverse events affecting the central nervous system observed during clinical trials is convulsions. Micro-electrode array (MEA) systems have recently attracted attention for use in evaluating the convulsion potential of a drug because they non-invasively measure the electrophysiological activity of neural networks at multiple sites in a high-throughput manner. Over twelve compounds including convulsants were tested at 5 concentrations. Using principal component analysis, clustering analysis, and artificial intelligence (AI), we have succeeded in separating the responses between convulsive drugs and negative control, and in classifying the mechanism of actions of drugs from spontaneous firing data. The MEA assay using hiPSC-derived neurons and our analysis method will be effective for predicting the seizure liability and mechanism of action of new drugs.

Joint Symposium

1-JS2-1

The significance and pifalls of the morphological techniques in pharmacological studies

Naoaki Saito[1]

[1]Kobe University Biosignal Research Center

Imaging techniques are indispensable methods for recent biological science. Japanese Society of Histochemistry and Cytochemistry is a society focusing on the advance of morphological tchniques and its appplication to life science. In this symposium, three morphology specialists introduce three important imaging techniques that is useful for pharmacological research.

1) Basic technique for immunocytochemistry and the pitfalls
2) Key techniques for multilabeling immunostaing using cultured cells
3) Imaging of physiological functions using fluorescent dye in living tissues

Joint Symposium

1-JS2-2
The principle and basis of immunohistochemistry

Hitoshi Ozawa[1]

[1]Dept.Anat. Neurobiol. Grad.Sch.Med., Nippon Med Sch.

Immunohistochemistry is extremely useful for exploring and visualizing specific substances present in cells, tissues, organs and individuals by utilizing diverse and specific molecular recognition mechanisms of the body called antigen-antibody reaction.
There are several important points in this step, but the first of which is to obtain and use a "good primary antibody". It is possible to detect substances (antigens) to be searched clearly, easily, and with high reproducibility by using a good primary antibody.
Secondly, we need to immobilize substances (antigens) present in cells and tissues by fixation. However, the task of fixation bridges between molecules or molecules within a molecule in proteins, nucleic acids, lipid molecules, and forms a state called polymer. It is also an important point of immunohistochemistry to make this contradictory phenomenon successfully compatible.
The third point is to visualize the antigen-antibody reaction. There are several visualization methods. It should be visible not only to look, but also specific, clearly judged.
It is important to make it possible to discriminate reliable immunohistochemical reaction while conscious of these points to prevent incorrect detection results and detection judgment.
In this presentation, I will explain the principle and basis of immunohistochemistry centering on the above three points.

Joint Symposium

1-JS2-3
Multi-colour immunoflourescence microscopy in cultured cells

Toshiyuki Matsuzaki[1]

[1]Dept. Anatomy and Cell Biology, Grad. Sch. Med., Gunma Univ.

Immunofluorescence microscopy is a powerful method for analysis of the subcellular localization of the protein of interest. The use of fluorescence is very effective for multiple labeling and for higher magnification observation with a laser confocal microscope as well as a conventional fluorescence microscope. The technique is easy and generally used for researchers; however, it is also true that they sometimes show the results inappropriately and incorrectly. I would like to introduce the basic methods with some helpful suggestions of the immunofluorescent staining in cultured cells, especially focusing on the followings:
1) Cell culture for immunocytochemistry
2) Fixation
3) Treatment before immunostaining
4) Key points for multiple labeling: choices of the secondary antibodies and fluorescence dyes
5) Observation and storage of the samples
I hope this talk could help researchers in the Pharmacological Society to get better and beautiful results in immunofluorescence microscopy.

Joint Symposium

1-JS2-4

Confocal microscopy - an emerging histochemical approach for integrated physiological understanding of living organisms

Hideo Tanaka[1]

[1]Dept. Pathol., Grad. Sch. Med., Kyoto Pref. Univ. Med.

Histochemistry, which enables us to visualize the precise distribution of target molecules within living organisms, is an essential strategy in life science research. Of various histochemical modalities, confocal microscopy provides not only the existence of target molecules, but also their spatiotemporal dynamics. Because of the high spatial resolution of the confocal images, fluorescence intensities for specific molecules reflect their concentrations: the higher the intensities, the more abundant the molecules present. In addition, rapid scanning confocal imaging provides precise concentration changes in functional molecules, reflecting cellular functions. Here I would like to exemplify fluorescent imaging of intracellular Ca^{2+} dynamics, cellular membrane potentials, and mitochondrial states of the cardiomyocytes in the heart. Photodynamic modulation of cellular functions will also be demonstrated.

1-YS-1
The Role of serotonin in emotion and decision making

Kazuki Nagayasu[1], Shuji Kaneko[1]

[1]Dept. Mol. Pharm., Grad. Sch. Pharm. Sci., Kyoto Univ.

Serotonin have been thought to play an important role in regulation of emotional states as well as decision making. Previously we have reported that the activity of the dorsal raphe serotonin neurons was increased by ketamine and olanzapine, promising therapeutic agents for treatment-resistant depression, as well as conventional antidepressants such as selective serotonin reuptake inhibitors and tricyclic antidepressants. It is, however, still unclear whether the activation of the dorsal raphe serotonin neurons is sufficient for eliciting antidepressant-like effects. Furthermore, identification of responsible serotonergic circuits for a variety of behaviors and disorders has been hampered by wide-ranging projection of serotonin neurons. To address these issues, we developed viral vectors capable of optogenetic manipulation of serotonergic neurons specifically. In this symposium, we would like to show our recent findings on the role of serotonin neurons in the regulation of mood and decision making.

1-YS-2

Repeated stress-induced behavioral changes and inflammation-like responses

Kitaoka Shiho[1], Xiang Nie[1], Kohei Tanaka[2], Atsubumi Ogawa[2], Eri Segi-Nishida[3], Shuh Narumiya[2], Tomoyuki Furuyashiki[1]

[1]Div. Pharm., Grad. Sch. Med., Kobe Univ., [2]Medical Innovation Center, Grad. Sch. Med., Kyoto Univ., [3]Dept. Biol-Sci and Technol., Faculty of Ind. Sci. and Technol., Tokyo Univ. of Sci

Stress is a risk factor for mental illness. Acute stress activates the sympathetic nervous system and HPA axis as a survival mechanism whereas prolonged and excess stress induces cognitive decline and behavioral abnormalities. For instance, repeated social defeat stress, an animal model of depression, induces behavioral changes such as social avoidance.

We previously reported that prostaglandin E_2 which is derived from microglia suppresses mesocortical dopaminergic pathway to induce social avoidance. However, we still do not know whether or how stress activates microglia, or whether microglial activation plays a role in stress-induced behavioral changes.

To identify a molecule which is induced by repeated social defeat stress in the medial prefrontal cortex (mPFC), we performed transcriptome analysis. Repeated social defeat stress upregulated S100A8 and S100A9 in the mPFC. These molecules form a heterodimer to exert their function. Intracellularly, S100A8/A9 migrates phagocytes in a calcium dependent manner. Extracellularly, S100A8/A9 activates Toll-like receptor 4 (TLR4). In this symposium, I will introduce the roles of TLRs in repeated stress-induced behavioral changes and the latest findings on inflammation-like responses.

1-YS-3

Orexin and fear; potential role of OX1R antagonist for treating anxiety disorders and PTSD

Shingo Soya[1]

Fear is an important physiological function for survival. It appears when animals or humans are confronted with an environmental threat. The amygdala has been shown to play a highly important role in emergence of a fear-related behavior such as freezing that only occurs when the environment contains some elements suggestive of danger. Previous studies showed that hypothalamic orexin neurons are activated by fearful stimuli to evoke a 'defense reaction' with an increase in arousal level and sympathetic outflow to deal with the imminent danger. However, how this system contributes to the emergence of fear-related behavior is still unclear. We took cued and contextual fear conditioning experiment using orexin 1 receptor knockout (*OX1R*$^{-/-}$) and orexin 2 receptor knockout (*OX2R*$^{-/-}$) and orexin double receptor knockout (*OX1R*$^{-/-}$*; OX2R* $^{-/-}$) and *prepro-orexin* knockout (*preproOX*$^{-/-}$) mice. We found that *OX1R*$^{-/-}$ and *OX1R*$^{-/-}$*; OX2R* $^{-/-}$ and *preproOX*$^{-/-}$ showed abnormality in both cued and contextual fear conditioning test suggesting the orexin system might be important for fear memory formation and/or consolidation and/or retrieval mainly via OX1R signaling. Orexin neurons in the hypothalamus send excitatory innervations to noradrenergic neurons in the locus coeruleus (NA^{LC}) which abundantly express OX1R and send projections to the lateral amygdala (LA), which is known as the critical region for fear memory formation. Opto/chemogenetic inhibition of this di-synaptic orexin $\rightarrow NA^{LC} \rightarrow$ LA pathway or pharmacological blockade of OX1R reduces cue-induced fear expression. Inversely, excitatory manipulation of this pathway after fear conditioning induces fear-related behavior. Although, fear memory helps animals respond precisely to a context or cue previously paired with an aversive stimulus, fear-related behavior is sometimes evoked even in a distinct context containing some similar elements, which is known as fear generalization. Our data suggests that the orexin $\rightarrow NA^{LC} \rightarrow$ LA pathway might explain a part of the mechanism of fear generalization. We also discuss about the potential effectiveness of OX1R antagonists for treating excessive fear response or overgeneralization seen in anxiety disorder and post-traumatic stress disorder (PTSD).

1-YS-4
Central histamine modulates learning and memory

Nomura Hiroshi[1]

[1]Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Hokkaido University

A method that promotes the retrieval of lost long-term memories has not been well established. Histamine in the central nervous system is implicated in learning and memory as well as sleep and wakefulness, feeding and drinking, and neuroendocrine regulation, and treatment with antihistamines impairs learning and memory. Since histamine H_3 receptor inverse agonists upregulate histamine release, histamine H_3 receptor inverse agonists may enhance learning and memory. However, whether H_3 receptor inverse agonists promote the retrieval of forgotten long-term memory has not yet been determined. Here, we employed multidisciplinary methods including the mouse behavior, calcium imaging and chemogenetic manipulation to examine whether and how the histamine H_3 receptor inverse agonists, thioperamide and betahistine, promote the retrieval of a forgotten long-term object memory in mice. The treatment of H_3 receptor inverse agonists induced the recall of forgotten memories even 1 week and 1 month after training in mice. In addition, we found a betahistine treatment promote memory retrieval in humans. These results highlight a novel interaction between the central histamine signaling and memory engrams.

Company-Organized Symposium

2-CS2-1
First FDA-approved Digital Medicine

Nobuyuki Kurahashi[1]

[1]Otsuka Pharmaceutical Development & Commercialization Inc

It is well known that there is a high correlation between the relapse rate of mental disorders such as schizophrenia and medication adherence. Therefore, it is possible to prevent acute exacerbation of symptoms and to prevent re-hospitalization by continuing taking medication. On the other hand, it is also well known that it is very difficult for patients to keep taking medication every day for various reasons - patients don't believe drugs work, troublesome side effects or lack of insights on their diseases.

It is very important to understand their medication adherence and their reasons non-adherence, we should provide enough support for them to continue their medication, raise awareness of their disease and educate them on the necessity and importance of taking their medication. However, it is not easy for healthcare professionals, care givers and families to know how good or bad the patient's adherence is because it depends on the patients self-report or checking of the residual medicine which is not always accurate. As a result, when the patient relapses, it is challenging for the healthcare professional to determine whether it comes from poor adherence or whether the medication is effective.

Otsuka and Proteus Digital Health (hereinafter referred to as "Proteus") developed the first digital medicine "Abilify MyCite" that can measure medication adherence. It embeds a very small sensor developed by Proteus into an antipsychotic Abilify tablet marketed by Otsuka. When a patient swallows tablets, a chip emits a signal in the stomach and it is captured by a small patch which sticks to the patient's abdomen and this is recorded. The patch transmits adherence information to the patient's smartphone as well as capturing activity and rest from sensors on the patch. The transmitted information is captured on both the patient's phone as well as shared with healthcare professionals, caregivers and families with the patients' consent. Based on this information, healthcare professionals can measure the condition of the patient and assess the risk if there is a sign of recurrence such as poor adherence or abnormal sleep pattern, then take the appropriate intervention.

In November 2017, Otsuka received approval from the US Food and Drug Administration (FDA) for this world's first digital medicine. We will continue to contribute to patients, families and healthcare professionals through not only medicines as a pharmaceutical company but also to provide important medical information and solutions for better patient health.

Company-Organized Symposium

2-CS2-2
Open innovation for Digital Health in Pharmaceutical industry

Norihiro Kikuchi[1], Shunichi Takahashi[1]

[1]Open Innovation Center Japan, Bayer Yakuhin, Ltd.

Digital Health has emerged as innovative technologies to transform healthcare industry. Many Digital Health solutions are being developed to solve the healthcare problems using artificial intelligence (AI), Internet of things (IoT), wearable devices etc. Pharmaceutical companies are also accelerating the development of Digital Health solutions to optimize their value chain from drug discovery to post marketing, and to improve patients' quality of life. Successful implementation of these solutions requires new competencies such as agile development and digital technological expertise, and open innovation is an essential part of fostering the competencies. At the presentation, we will share our digital activities and ‘G4A' which is an open innovation program for Digital Health.

Company-Organized Symposium

2-CS2-3
New trends in digitization in the pharmaceutical industry

Masaru Otsuka[1]

[1]Takeda Pharmaceutical

Recently, "digitization", a kind of buzz word, has been widely used in many industries. In addition, it has been estimated that "disruptive changes" would be induced by such a wave of digitization. The current trend gives me a lot of questions; The media has reported to use of digital technology advances in the health care industry, but what about? The media has reported that information technology (IT) companies have entered the healthcare industry, or what? How Google, Apple, Facebook, and Amazon (GAFA) have entered the healthcare industry? The changes in external environments have made sense for us in the health care sector？
In this symposium, I would like to disclose my understanding of "Implications of digital evolution for the pharmaceutical industry and future prospects", referring to the digital changes in other industries.

Company-Organized Symposium

2-CS2-4

Pharmaceutical Company and Cross-industry collaboration : Fusion & Future

Yurika Kino[1]

[1]Future Design Dept. Mitsubishi Tanabe Pharma Corporation

In 2017 Mitsubishi Tanabe Pharma established the Future Design Department. The Future Design Department is advancing a transformation to a data-driven company with a view to the use of Big Data, AI, IoT, Digital Medicine and other digital technologies with the objective of fostering "disruptive innovation" in the pharmaceutical business. We are working to create new methods that transcend the pharmaceutical industry's conventional pharmaceutical categories. Mitsubishi Tanabe Pharma is promoting open innovation with some universities and companies of different industries about issues with impact within the drug discovery value chain.

For example, Mitsubishi Tanabe Pharma and Hitachi have initiated collaborative creation for improving the efficiency of clinical trials using Hitachi's advanced digital technology such as AI.

In another example, in 2018, we will start an accelerator program. With the key words of "creating the future of healthcare" we will build a business model that transcends the conventional pharmaceutical business framework and strive to contribute to the happiness and health of patients and those around them.

In order to expand our business "around the pill" and "beyond the pill", we are working on the challenge of creating new value in the fields of medicine and healthcare through cross-industry collaboration with cutting edge technologies and different industries. In this presentation, we would like to introduce the above contents along the case of Future Design Department in Mitsubishi Tanabe Pharma.

2-ES2-1

Activation of the nursing education through atilizing the Model Core Curriculum for Nursing Education in Japan

Yukari Sugita[1]

[1]MEXT

In 2018, the number of nursing universities increased to 263 schools in Japan. One out of three universities have a nursing school, and nursing universities continue to increase.
Japanese nursing education in universities is facing many problems some of which are, difficulties in providing enough facilities, maintenance of the education level, estrangement from bachelor education and nursing practices after graduation, and reinforcement of abilities of evidence-based nursing practices.
Therefore, Ministry of Education, Culture, Sports, Science and Technology introduced the "Model Core Curriculum for Nursing Education in Japan" (MCCNE) in 2017. MCCNE aims at the acquirement of necessary and indispensable nursing competencies in the undergraduate course, which enumerates learning targets to be useful for making the curriculum.
MCCNE has 7 areas to develop qualities and abilities of a nurse for a lifetime. A is basic qualities and abilities required of a nurse. B is society and nursing science. C is basic knowledge for understanding people they care for, includes pharmacological science. D is basic nursing practice skills. E is basic nursing abilities to work in different areas of health care. F is clinical training, and G is nursing research. Clinical training should be integrated all of the areas.
We expect activation of the nursing education through utilizing MCCNE in Japan.

2-ES2-2
Review of planned education programs for medicine in nurses

Akiko Matsuda[1]

[1]Nara Medical University School of Medicine,faculty of Nursing

Among medical care incidents in Japan, an increase in medicine-related errors by nurses have been reported. These errors may be caused by a lack of knowledge of clinical pharmacology and drug interactions. It is important for nurses to acquire risk-management skills based on clinical pharmacology. In order to improve fundamental knowledge in clinical pharmacology for nurses, various training programs exist. We reviewed a number of educational programs in medicine and report our results.
Based on our results, it is necessary for medical education programs to include the following 5 essential elements: 1)An analysis of frequently-occurring medication errors in the field of clinical pharmacology, 2) an examination of therapeutic drugs for patient treatment and patient observation practices, 3) an emphasis on the pharmacokinetics and drug interactions between s and food/ drugs, 4) assessment of patient symptoms and risk-management and the drug efficacy, 5) the necessity of using the package inserts.
Effective methods for teaching include case studies and group discussions.

2-ES2-3

‘Pharmacists-Nurses coordination' - How to utilize the nursing viewpoint in pharmacotherapy -

Yasuo Takeda[1]

[1]Dept. Clinical Pharm., Kagoshima University H

The most important role of nurses as medical staff is "information practitioner" that provide patient information to other medical staff. Nurses are the most familiar medical staff to the patients when they are cure- and care-hospitalized. It leads to the best effect for the patient by conveying the information even if it is a trivial, obtained in daily relations with the patient to other medical professionals. In other words, nurses play a major role in "awareness" and "connecting" the information to medical staff to the changes in the condition of the patient. Recently, pharmacists reside in wards and administer medication therapy for hospitalized patients. But it is difficult to properly grasp the condition of all patients. In order for all patients undergoing medication to properly complete, the nurse is aware of the knowledge for the adverse drug reactions (ADRs) of each drug that patients take. It is very much important to notice its sign of ADRs in early and to prevent the severity of the ADRs by making appropriate treatment. In this symposium, I would like to talk about the importance of pharmaceutical knowledge and the Pharmacists-Nurses coordination for patient safety from the standpoint of pharmacists.

2-ES2-4

With the aim of improvement of quality and safety of medication by nurses - integrated Drug (iDrug) and simple guide of medication -

Toshihiko Yanagita[1], Ryuji Ikeda[2], Yasutoshi Hirabara[2]

[1]Dept. Clin. Pharmacol., Sch. Nursing, Fac. Med., Univ. Miyazaki, [2]Dept. Pharm., Univ. Miyazaki Hosp.

The installation of nursing universities has rapidly increased from the late 1990s, there are 263 institutions in Japan as of 2018. Pharmacology and Clinical Pharmacology education in undergraduate and postgraduate nursing universities is highly important, however, the lack of human resources involved in pharmacology education due to the rapid increase of nursing universities cannot be denied. The Ministry of Education, Culture, Sports, Science and Technology of Japan established a " Nursing education model･core･curriculum" for quality assurance of education at nursing universities in 2017. To meet the needs of a new phase of nursing education, re-examination of curriculum of Pharmacology education for nurses is necessary.

Doctors give prescriptions after considering the medical conditions of patients based on the concept of Personal drug (P-Drug). Pharmacists check the prescription, and give information about the effects of the drugs to the patients, including their side effects. Nurses observe patients to detect the effects and side effects of the administered drugs, and then report these to doctors and pharmacists. Each specialist plays a role, allowing medication to be completed. However, medication errors by nurses unfortunately caused because of lack of knowledge of therapeutic drugs.

In this symposium, I would like to propose a novel concept "integrated drug (iDrug)" and "simple medication guide" based on "Patient-oriented Pharmacology" for nursing Pharmacology education to maintain high level of safety medication.

Joint Symposium

2-JS3-1

Significance and future perspective of immunopharmacology from Japan

Masaru Ishii[1]

Drugs targeting the immune system have been widely exploited in the treatment of inflammatory, allergic and autoimmune disorders during the second half of the 20th century. The recent advances in immunopharmacological research made available new classes of clinically relevant drugs, comprising protein kinase inhibitors and biologics, such as monoclonal antibodies that selectively modulate the immune responses. ImmuPhar is the Immunopharmacology Section of IUPHAR, providing a unique international expert-lead platform aiming to dissect and promote the growing understanding of immune system as well as to challenge the identification and validation of drug targets and lead candidates for the treatment of many forms of debilitating immunological diseases. In this symposium I will outline the current movement on immunopharmacology in Japan as well as the activity of ImmuPhar, and discuss future perspectives in this trend.

Joint Symposium

2-JS3-2
Vascular endothelial cells, inflammation and HMGB1

Masahiro Nishibori[1]

[1]Dept. Pharmacol., Okayama Univ. Grad. Sch. Med.

High mobility group box-1 (HMGB1) was originally identified as an intranuclear chromatin DNA binding protein. HMGB1 has unique feature in its mobilization, translocation and release. Responding to ischemic/hypoxic and traumatic injuries, HMGB1 may be released from different types of cells through cytosolic compartment. In the previous studies, we demonstrated that HMGB1 was released from neurons by ischemic as well as hemorrhagic injuries in the brain, leading to the disruption of integrity of blood-brain barrier (BBB). Intravenous injection of anti-HMGB1 mAb protected BBB and ameliorated brain damage by reducing inflammatory responses including cytokine expression. In the epileptic animal model, we found that therapeutic anti-HMGB1 mAb administered systemically accumulated on vascular endothelial cells while protecting brain inflammation and neural damage. These findings strongly suggested that vascular endothelial cells may be one of major targets of anti-HMGB1 mAb action. In this symposium, I will show our recent data on HMGB1 mobilization in vascular endothelial cells induced by different stimuli, associated with cytokine production and cellular responses. The results imply that HMGB1 released from endothelial cells played fundamental roles in triggering inflammatory responses.

Joint Symposium

2-JS3-3

New aspect of immune pharmacology based on gut environment for the development of anti-allergic and anti-inflammatorv medicines

Jun Kunisawa

[1]CVAR, NIBIOHN

Intestines act as not only a digestive and absorption tissue of food but also as the largest immunological organ by containing various numbers and kinds of immunocompetent cells. Accumulating evidence indicates that that the functions of intestinal immunity are affected by gut environments such as dietary materials and commensal bacteria, which is tightly related to the development of immune diseases (e.g., allergy and inflammation) at various tissues. Recent technological advancements in the metabolome analysis, metagenomic analysis of commensal bacteria, and bio-informatics technology allow us to understand tripartite interaction between diets, commensal bacteria, and host immunity, leading to the establishment of new concept of drug design. In this talk, I will introduce our studies related to lipids derived from diets and commensal bacteria-mediated immune regulation and the application to the development of anti-allergic and anti-inflammatory medicines.

Joint Symposium

2-JS3-4

Anti-fractalkine antibody elucidates the roles of fractalkine-CX3CR1 axis in animal models

Toshio Imai[1]

[1]KAN Research Institute, Inc.

Inflammation and immune responses are evoked locally by invasion and accumulation of immune cells into the lesion sites. The cell trafficking of immune cells into the tissue from the blood is closely regulated by a number of cell adhesion molecules and chemotactic factors including chemokines.
Fractalkine (FKN)/CX3CL1 is a membrane-bound chemokine possessing a chemokine/mucin hybrid structure and has a dual function as an adhesion molecule and a chemoattractant. FKN is mainly expressed on activated endothelial cells and its cognate receptor, CX3CR1, is expressed on cytotoxic effector lymphocytes and monocytes/macrophages. To date, a lot of important roles of the FKN-CX3CR1 axis has been identified: (1) the rapid capture and firm adhesion, (2) chemotaxis, (3) the enhancement of the transmigration, (4) the patrolling behavior of monocytes, (5) the accessory cell function and (6) the cell survival.
In this symposium, we will overview the pathological roles of the FKN-CX3CR1 axis in several inflammatory and autoimmune disease models revealed by anti-FKN mAb, and its distinct mode of action from other cytokine inhibitors.

Joint Symposium

2-JS3-5
State-of-the art treatment strategy for rheumatic diseases

Yoshiya Tanaka[1]

[1]The First Dept. Internal Medicine, Sch. Med, Univ. Occupational and Environmental Health, Japan

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammation and joint destruction that causes significant morbidity and mortality. However, the combined use of methotrexate and biologics targeting TNF and IL-6 has revolutionized treatment of RA. Clinical remission is now realistic targets, achieved by a large proportion of RA patients, and rapid and appropriate induction of remission by the intensive treatment is prerequisite to halt joint damage and functional disabilities. Recently, orally available small molecules targeting Janus kinase (JAK) has taken in the therapeutic armamentarium in RA. Such a progress in treatments with biologics and JAK inhibitors of RA is now applied for various rheumatic diseases and systemic autoimmune diseases. Furthermore, treatment holiday of biologics is feasible in some patients with RA after maintaining deep remission by the intensive treatments, which has the potential of reducing adverse effects and medical costs as well as approaching to immunological remission. Finally, we currently try to treat patients with different biologics targeting TNF, IL-17 and IL-12/IL-23 based on the difference of lymphocyte phenotype. Such a treatment strategy should be guided by molecular, cellular and/or immunological mechanisms and a systematic approach to design a precision medicine to rheumatic diseases should help to achieve the goal.

Morning Seminar

2-MS1-1

Single-molecule localization based super-resolution imaging in the tissue specimens

Hirokazu Sakamoto

[1]Department of Pharmacology, Graduate School of Medicine, The University of Tokyo

Recent advances in super-resolution microscopy have overcome a limitation of spatial resolution in fluorescence imaging imposed by the diffraction of light, enabling nanoscale molecular imaging with conventional fluorescent probes. Single-molecule localization based super-resolution microscopy, including stochastic optical reconstruction microscopy (STORM), provides multi-color and three-dimensional imaging with a remarkable spatial resolution, and thus resolves detailed nanostructures in biological specimens. Fortunately, it can be performed with a simple wide-field microscope setup and is completely compatible with immunohistochemical fluorescent staining methods. In this seminar, I will talk a detailed method for STORM imaging, from sample preparation to image analysis, with some tips on how to improve the spatial resolution. I will then show some examples for STORM imaging of immunohistochemical specimens, including the brain and pancreas.

Morning Seminar

2-MS1-2

Tips on live-cell super-resolution microscopy and its application in RNA imaging

Tetsuro Ariyoshi[1], Yasushi Okada[1]

[1]Laboratory for Cell Polarity Regulation, RIKEN BDR

Recent advances in super-resolution microscopy has enabled diffraction-unlimited imaging of cellular structures and protein distributions in living cells. Many commercially available microscopes are now equipped with super-resolution mode, however, knowledge about how to choose an appropriate microscopy for each experiment is not shared among researchers yet. In this session we will introduce various types of state-of-art super-resolution microscopes with their actual applications and discuss about some critical points to notice when choosing microscopes for live-cell super-resolution imaging. We would also talk about our recent development of a novel live-cell RNA imaging tool and its application with super-resolution microscopy.

Morning Seminar

2-MS2

Drug discovery technologies to achieve pain relief through drug repositioning approaches

Tomohiro Yamashita[1]

[1]Laboratory of Global Healthcare, GraduateSchool of Pharmaceutical Sciences, Kyushu University

Neuropathic pain associated with cancer, diabetic neuropathy, chemotherapy or nerve trauma is an intractable chronic pain characterized by mechanical allodynia and abnormal pain hypersensitivity evoked by innocuous stimuli. Unfortunately, this disorder has no specific treatment. To discover potential new pain medications, I am merging high-throughput screening technologies with a drug discovery strategy that seeks new effects of approved drugs known as "drug repositioning". In this seminar, I will show that by using high-throughput Ca^{2+} imaging instrument, the compound duloxetine (a serotonin-norepinephrine reuptake inhibitor) inhibits the function of the purinergic receptor P2X4 (a subtype of ATP-gated non-selective cation channels), which is a potential therapeutic target for treating neuropathic pain. In addition, by using a newly established in vitro high-throughput phenotypic assay, we have discovered that fulvestrant (a drug for treatment of postmenopausal women with advanced breast cancer) exhibits a protective effect on oxaliplatin-induced neuronal damage and allodynia.

2-MS3

In vivo monitoring of neuronal activity with genetically encoded calcium indicators

Natsuko Hitora-Imamura[1]

[1]Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Hokkaido University

Observing neuronal activity of free-moving animals gives us a lot of information that helps us to understand the neural computations that mediate behavior. While many techniques have been utilized to measure neuronal activity in specific brain regions, these regions are made up of genetically and anatomically heterogeneous sub-populations, and dissection of neuronal activity of interest is still an ongoing challenge.

Neural activity causes rapid changes in intracellular free calcium. The development of genetically encoded calcium indicators, such as GCaMPs, allows us for in vivo visualization of calcium dynamics of specific neuronal populations. In this seminar, I will outline recent advances in calcium imaging technology, including fiberphotometry, and show our recent works on neural circuit mechanisms controlling appetitive and aversive learning.

Company-Organized Symposium

3-CS3-1

Evaluation methods for drug-induced seizure by applying microelectrode array recording to human iPS cell-derived neurons

Takafumi Shirakawa[1]

In the drug development in pharmaceuticals, development of drugs may be discontinued due to the toxicity and clinical side effect, therefore, safety assessment is one of the important factors in drug development. Recently, pre-clinical studies are screening for compounds by the in vitro screening system using human iPS cell-derived cells which are expected to predictively of human clinical. Human iPS Cell Applied Safety Assessment Consortium (CSAHi). CSAHi focuses on hepato-, cardio-, and neuro-toxicities as important toxicity organs which are attributed to the causes of discontinuation of drug development. In neurotoxicity, seizure is an important finding because of high frequency expression in nonclinical. Multi-electrode array (MEA) systems have recently attracted attention as useful for evaluating seizure risk because they can non-invasively measure the electrophysiological activities of neural networks. We are evaluating the electrophysiological responses to several seizure compounds using MEA in cultured hiPSC-derived neurons. It is important to establish an analytical method to detecting seizure-like activities. We have focused the periodicity of synchronized burst firings as one of the effective analytical parameters for detecting seizure risk. We identify the parameter sets that separate the responses between positive and negative compounds using principal component analysis of 10 parameters. The principal component analysis using parameter set focused on periodicity is useful method to detect the seizure risk.

Company-Organized Symposium

3-CS3-2

In vitro functional assay using human iPSC derived sensory neurons for drug side-effects detection

Ikurou Suzuki[1]

[1]Dept. Electronics., Grad. Sch. Eng., Tohoku institute of Tech.

Functional assays using human induced pluripotent stem cell (hiPSC)-derived sensory neurons are expected to predict the drug safety and side effects in human peripheral nervous system. However, evaluation assays in hiPSC-derived sensory neurons has not been established, and electrophysiological response to pain-related molecules are not known. In this study, we aimed to evaluate the physiological responses to pain-related molecules including anti-cancer drugs in cultured hiPSC-derived sensory neurons using high-throughput multi-electrode array (MEA) system. In capsaicin, menthol, and AITC administration, evoked responses depending on TPRV1, TRPM8, and TRPA1 channel were detected, respectively. We found that hiPSC-derived sensory neurons are a heterogeneous cell population that have different responses to temperature and pain molecules, like living body. Cold hypersensitivity responses were also detected in concentration dependent manner of anti-cancer drug oxaliplatin. These results indicated that this MEA evaluation method using human iPSC-derived sensory neurons is effective as a pain-related toxicity in human peripheral nervous system.

Company-Organized Symposium

3-CS3-3
Drug-induced seizure liability screening based on a locomotor activity assay in zebrafish

Akihito Yamashita[1], Jiro Deguchi[1], Izuru Miyawaki[1]

As drug-induced seizures have severe impact on drug development, evaluating seizure induction potential of candidate drugs at the early stages of drug discovery is important. A novel assay system using zebrafish has attracted interest as a high throughput toxicological *in vivo* assay system, and we have established an experimental method for drug-induced seizure liability on the basis of locomotor activity in zebrafish. Our established experimental method included monitoring locomotor activity at high-speed movement (> 20 mm/sec), extending exposure time or conducting flashlight stimulation (10 Hz) which is a known seizure induction stimulus. The validation study using our methodology was used to assess 52 commercially available drugs, and the prediction rate was approximately 70%. The experimental protocol using zebrafish is considered useful for seizure potential screening during early stages of drug discovery.

Company-Organized Symposium

3-CS3-4

CNS preclinical studies for drug development are becoming substantial in the world

Kaoru Sato[1]

[1]Lab Neuropharmacol, Div Pharmacol, NIHS

At present, owing to the species differences, we have little options for preclinical studies to predict adverse effects (AEs) in the human CNS. However, as introduced in this symposium, a series of new *in vitro* experiments have been developed to improve the predictability of CNS AEs. This trend is not limited to Japan inside, but also seen worldwide. Our research project 'iPSC Non-Clinical Experiments for Nervous System（iNCENS）', aiming at the establishment of the evaluation systems to predict seizure risks of new drugs, is now a committee member of an international think tank, International Life Sciences Institute (ILSI), Health and Environmental Sciences Institute (HESI), NeuTox micro-electrode array (MEA) sub team. Most megapharmas and regulatory agencies are participating in the pilot study to clarify the efficiency of the electrophysiological recordings of MEA. We are providing some promising data recorded from hiPSC-neurons. In this symposium, I will introduce our on-going activities together with the global trends concerning the development of preclinical *in vitro* evaluation systems to predict CNS AEs.

Company-Organized Symposium

3-CS4-1
AI and drug discovery

Kazuhisa Tsunoyama[1]

[1]Astellas Pharma Inc., Real World Informatics and Analytics function, Analytics and Informatics

We are now facing the third wave of artificial intelligence (AI). AI refers to simulated intelligence in machines that have been programmed to mimic human brain behavior such as learning, reasoning and problem solving. Many computer algorithms had contributed to previous waves, but this latest wave of AI was created by deep learning algorithm which is inspired by how human brain processes information through interaction of neurons. The first simplified mathematical model of neuron, the formal neuron, was proposed by McCulloch and Pitts in 1943. In this model, a neuron receives a set of binary inputs from other neurons, multiplies each input with the weight (i.e. the strength of synapse), and activates if the sum of these weighted inputs is greater than a threshold. More than 70 years have passed since this simple model was proposed and we are now seeing many examples where AI beats humans. In this symposium, we have speakers from two pairs of pharmaceutical and IT companies that have recently announced big partnership for AI technology, and they will present their recent development and application of AI, and their future prospects. I hope we can learn many cases of applications of AI to biology, pharmacology, drug discovery, and pharmaceutical business.

Company-Organized Symposium

3-CS4-2
Opportunities for artificial intelligence in a pharmaceutical company

Nobuya Ishii[1]

[1]Dept. Science & Technology Intelligence, Project & Lifecycle Management Unit, Chugai Pharmaceutical Co., Ltd.

After a lot of initial artificial Intelligence (AI) hype, many useful AI applications have been identified, and now AI is transforming many industrial areas. Pharma companies also realize the application of AI can positively disrupt the traditional business processes in various ways, such as smarter therapy target hunting, quicker drug candidate molecule generation, efficient non-clinical/ clinical development, and more precise drug market penetration. Currently many pharma companies are actively trying to apply AI technologies to their business. However, before AI implementation into their business processes, pharma companies need to make some decisions on how to approach to AI technologies, such as collaborations with AI companies or internal development of AI capabilities. In this session, points needed to be considered upon collaborations with AI companies from pharma perspectives will be discussed. Also, potential applications of AI to pharmaceutical business processes will be discussed including some real use cases.

Company-Organized Symposium

3-CS4-3
Deep Learning for Drug Discovery

Ryuuitirou Ishitani[1]

[1]Preferred Networks, Inc.

Deep learning has dramatically improved in recent years and has achieved breakthrough results in image recognition, speech recognition, machine control, anomaly detection, etc. In the field of biotechnology and life science, deep learning is widely used. Deep learning is a promising technology in the field of biotechnology and life sciences for its ability to extract useful features in its process of learning, achieve multi-modal and multi-task learning naturally, and successfully handle data on genomic sequence, low molecular weight compounds, and protein, which are of varying size. In this presentation, we will introduce the latest applications of deep learning and explain how deep learning can be used in the process of drug discovery.

Company-Organized Symposium

3-CS4-4
Cases in Mitsubishi Tanabe Pharma

Masataka Kuroda[1]

[1]Modality Laboratories, Mitsubishi Tanabe Pharma Corporation

To accelerate the drug-discovery and -development stages, one of solutions is to shorten the term of each task contained in the stages. AI has potential to solve this issue and has been applied to several tasks. Furthermore, some AI systems are in development. I will introduce three examples in the drug-discovery stage and one in the development stage, 1: Prediction of human cardiotoxicity, 2: Phenotype screening derived from cell morphological image features, 3: ADMET prediction for the designed compounds, 4: Efficiency improvement of clinical trials collaborating with Hitachi. Hitachi will talk about the fourth one in detail. The aim of these examples is to reduce time-consuming works, to compensate experimental data with highly accurate predictions, or to possess better observing-eyes instead of human eyes.

Company-Organized Symposium

3-CS4-5
Artificial Intelligence in Clinical Development

Kunihiko Kido[1]

[1]Hitachi, Ltd., Research & Development Group

Clinical trials are time consuming, expensive, and often burdensome on patients. Poor protocol design can reduce a success rate of clinical trials. In order to improve protocol design, pharmaceutical companies often spend a lot of time searching for information thoroughly regarding protocol design. In the past years, we have dedicated tremendous efforts to explore and implement novel Artificial Intelligence (AI) applications to advance clinical development. During these projects with Mitsubishi Tanabe Pharma, we have gained experiences with developing AI applications. Especially, we're focusing on AI applications for protocol design. In these applications, we're leveraging NLP & Deep Learning to help pharmaceutical companies optimize their protocol designs. Our system learns from all kinds of sources, like ClinicalTrials.gov, past clinical trials, journal articles and provide recommendations for clinical trial optimization. This presentation will discuss our early findings on the AI in protocol design.

3-CW-1
Development of *microminipigs* and their electro-pharmacological characteristics

Atsushi Sugiyama[1,2], Mihoko Hagiwara-Nagasawa[1], Ai Goto[2], Koki Chiba[2], Ryuichi Kambayashi[1], Hiroko Izumi-Nakaseko[1,2], Atsuhiko T. Naito[1,2]

[1]Dept. Pharmacol., Faculty Med., Toho Univ., [2]Dept. Pharmacol., Grad. Sch. Med., Toho Univ.

In vivo studies are mandatory to confirm whether a principle generated from *in vitro* experiments can be reproducible under physiological and pathological conditions, which has become difficult to perform under the principles of 3Rs for animal welfare. Pigs have been expected as an alternative laboratory animal; however, neither regular pigs nor miniature pigs may be suitable for confirming *in vivo* proof, since they need larger dosage of expensive test articles under developmental phase. Lately, extraordinarily small-sized miniature pigs; namely, *microminipigs*, weighing approximately 7 kg at 6 months of age when they are young mature, were developed by Fuji Micra Inc. (Shizuoka), which have been provided to several research organizations in Japan as a non-rodent experimental animal optimized for life-science research. We have characterized *microminipigs* by assessing cardiovascular effects of various drugs and medical devices, and found that most of the cardiovascular responses observed in *microminipigs* were similar to those in human subjects as well as other non-rodent animals. In this workshop, we will present a brief summary of the development of *microminipigs* along with recent publications of it in the field of cardiovascular physiology/pharmacology.

3-CW-2

Approach to pharmacological studies using pigs for drug discovery

Toshiyuki Maki[1], Minori Ikehata[1], Hiroaki Yoshioka[2], Tomoki Shimada[2], Noriyasu Sano[3], Teruki Hamada[3], Keiko Igaki[1], Tomonori Kitaura[1], Maya Mukaitani[1], Manami Kaneko[1]

[1]Integrated Biology Research Division, Axcelead Drug Discovery Partners, Inc., [2]Non Clinical Safty Research, Axcelead Drug Discovery Partners, Inc., [3]Drug Disposition & Analysis, Axcelead Drug Discovery Partners, Inc

Axcelead Drug Discovery Partners, Inc. (Axcelead) was separated from Takeda Pharmaceutical Company Limited and established in July, 2017 to support drug development of academia, pharmaceutical companies, and startups. We provide various services including drug screening, compound synthesis, pharmacological studies, pharmacokinetics examinations, and toxicological studies. We put great efforts into developing large animal models including pigs as pharmacological studies with large animals are desired in the area of regenerative medicine such as cell therapy. An original immunosuppressed pig model has been developed by two methods at Axcelead. The first is to remove thymus and spleen which regulate immune system in pigs. The second is to utilize immunosuppressive agents, which we measure those concentrations in plasma and control dosages to reach the targeted plasma concentration. The targeted concentration in vivo is decided based on in vitro assay using peripheral blood mononuclear cells isolated from pigs and calculated protein binding rate. To reduce stress for animals, the drug is administered via gastrostomy and blood samples are collected from central venous catheter. Furthermore, heart failure and type 1 diabetes pig models have been developed at Axcelead. We will introduce our immunosuppressed models and the two disease models at this workshop.

Company-Organized Workshop

3-CW-3
Application Examples of Pigs in the Field of Pharmacology Study - Centering on Bone Metabolism Test and Implantation Test -

Azusa Seki[1]

[1]Hamri Co., Ltd.

Pigs are occasionally used in toxicity and pharmacology studies in European countries but rarely in Japan. On the other hand, in pharmacology studies, pigs have been used in skin irritation and absorption tests as one of the alternate animals. However, in recent years, the production of min-pigs maintained under the quality management has been established in Japan and these animals are used actively in each field. The accumulation of the basic data for mini-pigs increases steadily and pigs are used while confirming whether the projects can be correctly conducted only in pigs each time.

Pigs (including training pis) weighing about 10 mg - about 100 kg can be obtained as experimental animals. The body weights of these animals are within the range of human body weights and the conditions capable of coping properly with various variations such as thickness of the blood vessels, size of the visceral organs, load on the joints can be satisfied in pigs. Therefore, pigs are useful animals in preclinical studies. Pigs are remodeling animals showing the bone metabolic turnover similar to that in humans. Since the implantation of bones into the long bones is actively conducted, soft bones such as meniscus and intervertebral disc are actively used in these animals and the sizes of these bones are appropriate for performing the surgical treatment, the use of pigs is more recommendable than that of rabbits, dogs and monkeys and pigs have advantages in evaluating the test substance clearly over the other animals.

In the field of dentistry the use of pigs are also gradually started but since there are still difficulties in obtaining appropriate thickness of the skull and extracting the teeth, the preparation of animal models and the evaluation of the test substance are now in the process of trial and error.

As for the visceral organs, pigs are actively used in the field of transplantation and especially in the circulatory system, kidneys and vascular system. In the extrapolation to humans, many organs of pigs are similar to those of humans in eating habits and anatomical features and are similar to those of humans in the size of organs. Therefore pigs are highly useful in preclinical studies.

On this occasion, we would like to investigate the usability and usefulness of pigs further through the introduction of part of cartilage regeneration test, bone implantation test and validation test for prevention of visceral adhesions which are performed in our Tsukuba Research Center.

3-ES3-0

[Overview] Future prospects of pharmacology education programs in medical school

Yoshio Goshima[1]

[1]Department of Molecular Pharmacology and Neurobiology, Yokohama City University Graduate School of Medicine

It is widely recognized that the concept of core curriculum with options is a response to the major problem of content overload. Pharmacology education systems in medical schools are continuously challenged to reform in Japan as well as other countries. The goals of medical workers in patient management are optimization of the pharmaceutics for their patients. To this aim, various new trials have now being conducted. We'll discuss future prospects of pharmacology education keeping designing a next-generation education system in mind.

3-ES3-1

Nationwide Survey Results of the Lectures and Practice Conducted in the Department of Pharmacology or Clinical Pharmacology in Medical Schools

Masaki Mogi[1]

[1]Department of Pharmacology, Ehime University Graduate School of Medicine

There are few nationwide reports on pharmacology education to show actual total school hours, how to evaluate students' knowledge, what textbook is recommended to students, or what are performed as pharmacological practice etc. The present study investigated such facts on pharmacology education, based on the results of a nationwide survey asked to the chiefs in the Department of Pharmacology or Clinical Pharmacology in Medical Schools. Around 70 percent of total invited chiefs replied to the survey with answering many kinds of questions. Currently, data have being aggregated. For example, average total school hours are around 90 hours per year. Examination is mainly performed by a combination of description-type and multiple-choice questions. Main textbook is recommended but not specified in a half of the facility. Staffs spend 28 hours for the pharmacological practice per year, etc. Overall, survey results exhibited that the chiefs in the Department of Pharmacology or Clinical Pharmacology in Medical Schools are suffering from performing long-time lecture and pharmacological practice with fewer staffs, but continuously make efforts to perform better pharmacology education with worrying about properly evaluating such educational efforts from the executive in the school. I will discuss about the future plan for pharmacology education with taking into consideration of nationwide cooperation in this session.

3-ES3-2

A scheme for laboratory exercises led by undergraduate students

Chihiro Yabe[1]

[1]Dept. Pharmacol., Kyoto Pref. Univ. Med.

To maintain the quality of education in laboratory training with limited human resources, we developed an original method to carry out exercises led by undergraduate students themselves. Our concept is to let all students play individual roles during the seven-day exercises in pharmacology. Laboratory exercises are mainly animal studies using mice and guinea pigs, or a computer simulation of therapeutic drug monitoring. Each student is primarily allocated to a distinct role in the practice of his/her own choice. Faculty members coach the students assigned to respective exercises in advance, so that they learn how to guide their group on the day of practice. With the usage of this "YANEGAWARA" system, laboratory exercises in a large number of students could be operated under the supervision of a few faculty members. Detailed scheme of our trial will be presented at the symposium.

3-ES3-3

Use of movies as practical training / exercise teaching materials, entitled “Cine-Pharmacology”.

Norio Sakai[1]

[1]Graduate School of Biomedical & Health Sciences

We are using movies as a secondary task of pharmacology practice. We show several movies suitable as a teaching material of pharmacology or medicine and let students to write a report on drugs and treatment used in the movie. The suitable examples contain Beautiful mind, The awaking, Rain man and Patch Adams and so on. These movies are also useful as education of medical ethics. In this symposium, we will discuss this subject using concrete examples.

3-ES3-4

Simulator-based pharmacological practice using iPad-Cloud system for medical education

Koichiro Wada[1], Haruki Usuda[1], Tetsuya Tanaka[1], Takayuki Okamoto[1]

Pharmacological practice is important for understanding pharmacological effects from the point of view of active learning in medical education. However, it is very difficult to perform the practices using experimental animals in recent years, because of animal welfare, cost and so on.
We, therefore, developed novel simulation system for animal pharmacological practice using iPad. In our system, each student can access to the Cloud using iPad and simulate the situations for application of various drugs and reagents to atrium, ileum and circulation in whole animal. In addition, students are given various assignments about the pharmacological effects of drugs and reagents and try to solve them. Reports from students about the simulator are prepared by the processes to solve the assignments and their results. Therefore, our system is one of the "problem-based active learning" system.
It is difficult for complete replacement of animal-based pharmacological practice to simulator-based one in present time. However, our simulation system may be useful for reduction of the number of animal use in pharmacological practice.

3-JPS-1

Targeting ER-mitochondria communication through sigma-1 receptor ligands in physiopathology and neurodegenerative disorders

Tangui Maurice[1]

[1]MMDN, Univ Montpellier, INSERM, EPHE, UMR_S1198

Endoplasmic reticulum (ER)-associated mitochondrial membranes (MAMs) are highly functionalized domains of interaction between ER and mitochondria in the cells, stabilized by proteic bridges and sequestering numerous proteic assemblies. Through MAMs, ER and mitochondria exchange Ca^{2+}, proteins, lipids or small signaling molecules. Ca^{2+} exchanges are driven by IP_3 receptors (IP_3Rs) on ER and VDAC1/MCU complexes, mNCS, UCPs, and Letm1 on mitochondrial membranes. MAM dysfunctions are responsible of several mitochondrial diseases or genetic syndroms, and directly contribute to the neurodegenerative processes in Alzheimer, Parkinson, Huntington diseases and amyotrophic lateral sclerosis.

Targeting MAMs fonctionality by drug candidates is a novel pharmacological area of research and it may offer effective and potentially wide spectrum therapeutic strategies. We are interested since several years in developing drug candidates targeting the sigma-1 chaperone protein (S1R). Highly expressed in MAMs, S1R interacts with IP_3Rs, ER stress sensor proteins (BIP, IRE1), or steroids (pregnenolone) to potentiate focused Ca^{2+} exchanges between the organelles, stabilize mitochondrial physiology (particularly by interacting with complex I) and maintain MAM integrity. We will here detail the physiopathological importance of targeting MAMs and describe new drug development programs with new S1R agonists or positive modulators that already showed very promising efficacy in several neurodegenerative pathologies.

Keywords:
ER-mitochondria communication; sigma-1 chaperone protein; drug development; neurodegenerative diseases.

3-JPS-2

An experimental approach using a neurosteroid deficient mouse model from Kampo medicines to autism spectrum disorder (ASD) therapy

Kinzo Matsumoto[1], Hironori Fujiwara[1]

[1]Div. Medicinal Pharmacol., Inst. Natural Med., Univ. Toyama

ASD is a developmental disorder with core symptoms of social impairments and restrictive repetitive behaviors. Its prevalence in a male is 4-times higher than in the female. Dysfunction in the GABAergic system has been implicated in ASD but the exact cause is unclear yet. Thus, no appropriate drugs are currently available for ASD. We recently found that SKF105111 (SKF), a type I 5α-reductase inhibitor, reduced the brain level of allopregnanolone (ALLO), a positive allosteric $GABA_A$ receptor modulator and thereby caused ASD-like behaviors only in male mice, suggesting that SKF treatment provides a novel animal model of ASD. Moreover, to elucidate if Kamishyoyosan (KSS), a Kampo formula used for the treatment of neuropsychiatric symptoms in the menopause female, is available for ASD therapy, we examined the effects of KSS on ASD-like behaviors in the ALLO deficient mouse model. KSS ameliorated sociability deficits via improving the mechanisms mediated by the dopamine D_1 receptor, while it reduced repeated grooming behaviors via improving the mechanisms mediated by dopamine D_1 and D_2 receptors and the $GABA_A$ receptors. Our findings suggested that KSS is beneficial for the treatment of ASD.

3-JPS-3
Mast cells as therapeutic target in non-atopic diseases

Redegeld Frank[1]

[1]Div Pharmacol, Utrecht Inst Pharmaceut Sci,Facul Sci,Utrecht Univ, Netherlands

Mast cells are crucial effector cells in allergic reactions, where IgE is the best-known mechanism to trigger their degranulation and the release of allergic mediators. Mast cells are also found activated in inflammatory conditions such as autoimmune diseases, chronic inflammatory conditions in upper and lower airways, intestine and skin, neuroinflammation, and cancer, conditions generally not paralleled with an increased antigen-specific IgE expression. However, mast cells can be activated by numerous other stimuli such as complement factors, toll-like receptor ligands, neuropeptides, cytokines, sphingolipids, ATP/ADP/adenosine, histamine and various exogenous compounds. Previously, we have shown that immunoglobulin free light chains (FLC) may also trigger antigen-specific mast cell activation in the absence of IgE. FLC were shown to be increased in various inflammatory disease such as rheumatoid arthritis, non-allergic rhinitis, COPD, inflammatory bowel disease, and cancer and correlated with disease activity. In various preclinical models, we demonstrated that FLC may be of importance to induce mast cell activation and the onset of an inflammatory response. Interestingly, current experiments indicate that FLC may synergize with IgE to stimulate mast cell degranulation. Under conditions of minimal mast cell stimulation via IgE-receptor crosslinking, co-stimulation with FLC strikingly enhanced mast cell activation. These novel findings suggest that this synergy may be relevant under conditions of low local or systemic IgE production.
Keywords: mast cell, IgE, immunoglobulin free light chain, allergy, inflammatory diseases, cancer

3-JPS-4

Phosphatase SHP2-mediated mitochondrial homeostasis for the resolution of inflammation*

Xu Qiang[1]

[1]State Key Lab Pharmaceut Biotech,Sch Life Sci,Nanjing Univ, China

The negative regulation of inflammation is very important for the resolution of inflammatory diseases. Although many components and mediators in inflammation have been identified, how inflammation is finely regulated remains lack of evidence. Here we show that Src homology-2 domain containing protein tyrosine phosphatase-2 (SHP2) translocates to mitochondria in the early time of inflammatory stimulation. The RRWFH motif in SH2 domain is essential for the translocation of SHP2. This phosphatase finally localizes in the mitochondrial matrix with the help of Tom20/Tom40 in outer membrane and Tim23 in inner membrane. Then SHP2 interacts with ANT1, a central molecule controlling mitochondrial permeability transition. This mechanism prevents the collapse of mitochondrial membrane potential, mtDNA release and ROS production, and thus inhibits the hyperactivation of NLRP3 inflammasome. Ablation or inhibition of SHP2 in macrophage causes intensified NLRP3 inflammasome activation, production of IL-1β and IL-18, and increased sensitivity to peritonitis. Collectively, our data highlight that SHP2 orchestrates an intrinsic regulatory loop for the mitochondrial homeostasis to limit excessive NLRP3 inflammasome activation, suggesting a possibility to treat inflammatory diseases via maintaining mitochondrial homeostasis.

*This study is supported by National Natural Science Foundation of China (81330079 and 81730100).

Key words: SHP2, resolution of inflammation, mitochondrial homeostasis, NLRP3 inflammasome.

3-JPS-5
Current and future targets of pharmacotherapies for lower urinary tract dysfunction

Naoki Yoshimura[1]

[1]Dept. of Pharmacology & Chemical Biology and Dept. of Urology, Univ.of Pittsburgh, USA., [2]Dept. Urology, Sch. Med., Univ. Pittsburgh

The functions of the lower urinary tract, to store and periodically release urine, are organized by complex central and peripheral neural control mechanisms. Thus, various disease conditions in the central and peripheral levels can produce lower urinary tract symptoms (LUTS) such as urinary urgency, incontinence or voiding difficulty, urinary retention. Currently, standard pharmacotherapies for overactive bladder (OAB) include muscarinic receptor antagonists and, more recently, $beta_3$-adrenoceptor agonists and for male LUTS due to benign prostatic hyperplasia (BPH) utilize $alpha_1$-adrenoceptor antagonists. Phosphodiesterase type 5 (PDE5) inhibitors and 5alpha-reductase inhibitors have also been prescribed for BPH-associated male LUTS. Furthermore, based on the pathophysiology of LUTS, new pharmacological targets have been identified in bladder urothelium-afferent pathway interactions (e.g., P2X, PGE2 receptors), the spinal cord (e.g., serotonin, glycine system) and the brain (e.g., adenosine, CRF system). In addition, a new chemogenetic approach using "DREADD" may be useful to achieve the subpopulation-specific silencing of sensory pathways using designer receptors with synthetic ligands for the LUTS treatment without affecting the endogenous system.

Joint Symposium

3-JS4-1
Gut microbiota opens the future of cancer immunotherapy

Kiyoshi Yoshimura[1], Kazuyuki Hamada[2], Makoto Taniguchi[1], Yuya Hirasawa[2], Midori Shida[1], Takashi Manzaki[1], Hiroo Ishida[2], Yutaro Kubota[2], Junji Tsurutani[3], Satoshi Wada[4], Takehiko Sambe[5], Naoki Uchida[5], Yuji Kiuchi[6], Shinichi Kobayashi[7], Takuya Tsunoda[2]

[1]Dep. of Clinical Immuno-oncology, CRI of Clinical Pharm., Showa University, [2]Division of Medical Oncology, Department of Med., Showa University, [3]Advanced Cancer Translational research institute, Showa Univ., [4]Dep. of Clinical Diagnostic Oncology, CRI for Clinical Pharma., Showa Univ., [5]Div. of Clinical Pharm., Dep. of Pharm., School of Med., Showa Univ., [6]Div. of Medical Pharm., Dep. of Pharm. School of Med., Showa Univ., [7]Clinical Research Institute of Clinical Pharmacology and Therapeutics, Showa University

The development of cancer immunotherapy is the history of activation of its immune system, however it is also the history of failure of the development of the therapy. In these histories, the concept of immune checkpoint was born resulting a big breakthrough. While many excellent fundamental researches have not reached clinical application, checkpoint inhibitors succeeded in translational research and drug discovery. Since anti-PD-1/PD-L1 blockade therapy has been delivered to the world, types of tumor were divided into two groups. One is sensitive type by immunotherapy called as Hot tumor, and the other one is the other way called as Cold tumor which is difficult to demonstrate effectiveness. In recent years it has become clear that the gut microbiota has a great influence in terms of tumor immune microenvironment. We are actively pursuing analysis of gut microbiota with cases of treatment by cancer immunotherapy and chemotherapy. The development of this research is boosted by improvement of the next generation sequencer and analysis method. In addition to this, we also add non-linear analysis by adding Artificial Intelligence (AI) to analytical methods. These results will be used for future fecal transplantation as a translational research. We introduce our new findings, explain the trend of the development of cancer immunotherapy in the world, and we will state what kind of action we are taking for it.

Joint Symposium

3-JS4-2

Patients supported drug discovery and development for neurological incurable disease termed HTLV-1-associated myelopathy (HAM)

Yoshihisa Yamano[1]

[1]Department of Advanced Medical Innovation, St. Marianna University School of Medicine

Some infected with human T-lymphotropic virus type 1 (HTLV-1), which causes adult T cell leukemia/lymphoma (ATL), develop the neuroinflammatory disease HTLV-1 associated myelopathy (HAM). Suffering from progressive spinal cord paralysis, HAM patients experience a low quality of life with high unmet needs. Since the prognosis for HAM patients is extremely poor, there is a strong demand for a novel therapeutic strategy. Therefore, we established a national patient registration system (HAM-net) in collaboration with patient groups to gather data from and distribute information to patients on a nation-wide scale. By establishing a registration system for HAM patients, we have learned more about the variation in the rate of HAM progression that enables to divide patients into groups based on progression speed and compare attributes between groups. In addition, we recently showed that HTLV-1 mainly infects CCR4+ T-cells and causes functional abnormalities that are believed to drive HAM pathogenesis. We next demonstrated that anti-CCR4 antibody is effective at reducing the proviral load and inflammatory response in PBMCs from patients with HAM. Given the overwhelming evidence to support the idea that anti-CCR4 antibody could benefit HAM patients, we began an Investigator-led clinical trial. The phase 1/2a trial of the anti-CCR4 antibodies proceeded smoothly; in January 2016, the clinical studies were completed, and a proof of concept of the safety and efficacy of the treatment was obtained (*N Engl J Med, 2018*).

Joint Symposium

3-JS4-3

Development of pharmacotherapy for pediatric liver diseases with chronic intrahepatic cholestasis

Hisamitsu Hayashi[1]

[1]Lab. Molecular pharmacokinetics, Grad. Sch. Pharm. Sci., Univ. of Tokyo

Bile salt export pump (BSEP, encoded by *ABCB11*), an ABC transporter localized on the canalicular membrane (CM) of hepatocytes, mediates biliary excretion of bile acids (BA). Its dysfunction impairs bile formation, a liver condition called intrahepatic cholestasis (IC). PFIC2, the most severe form of IC caused by mutation in *ABCB11*, progresses to liver failure and death before adulthood. Currently, the only therapeutic approach is liver transplantation.

We have shown that PFIC2-causing mutations predominantly affect expression of BSEP on the CM but not its transport activity and then searched potential compounds to restore BSEP expression. Sodium 4-phenylbutyrate (NaPB), a drug approved for urea cycle disorder (UCD), was found as the candidate. Animal experiments and retrospective study in UCD patients indicated that treatment with NaPB increases BSEP expression on the CM and thereby its function. Clinical study in three PFIC2 patients showed that NaPB therapy markedly improved biochemical tests, clinical symptoms, and liver histology.

Based on these facts, we have started clinical trial to obtain approval for new indications of NaPB for PFIC2 (UMIN000024753) and clinical study to investigate therapeutic potency of NaPB in patients with IC other than PFIC2 (UMIN000027666).

3-YS-1
Cortico-thalamic reciprocal circuit working for trigeminal sensory processing

Takahiro Furuta[1]

[1]Dept. Oral Anatomy and Neurobiology, Grad. Sch. Dentistry, Osaka Univ.

Primary sensory cortexes provide massive descending axons to the thalamus to modulate sensory responsiveness of thalamic relay neurons. These top-down controls are pivotal for shifting neuronal firing between burst and tonic modes. The impact of the corticothalamic pathways on the firing mode and sensory gain of thalamic neurons has only been extensively examined in anesthetized animals, but has yet to be established in the awake state. We investigated what change were caused by lesions of the barrel cortex in responses of thalamocortical and thalamic reticular neurons to a single vibrissal deflection during wakefulness. Our results showed that the cortical lesions shifted the response of thalamic neurons towards bursting, elevated the response probability and the gain of thalamocortical neurons, predominantly of recurring responses. In addition, after the lesions, the spontaneous activities of the vibrissa-responsive thalamic neurons were typified by rhythmic spiking with frequent bursting. In single neuron recording/labeling experiments, layer 6 corticothalamic neurons responded to a single vibrissal deflection with short latencies in awake rats, strongly suggesting the existence of an immediate corticothalamic feedback. Because these results showed the importance of corticothalamic neurons in shaping thalamic activities during wakefulness, we next explored what neural circuits in the cortex affected the activities of the corticothalamic circuits. We will further present morphological analyses of corticocortical networks which input to the barrel cortex.

3-YS-2
Monitoring bidirectional information processing between neurons and astrocyte

Eiji Shigetomi[1], Schuichi Koizumi[1]

[1]Dept. Neuropharmacol., Interdiscipl. Grad. Sch. Med., Univ. Yamanashi

Astrocytes intimately contact synapses with their fine astrocyte processes regulating synaptic functions. Fine astrocytic processes can receive information from synapses and also transmit their information to synapses. Thus, astrocytes may regulate synapses through bidirectional information processing. Recently, we found astrocytes regulate synapse remodelling in primary somatosensory cortex in Ca^{2+} dependent manner, contributing to the induction of aberrant sensation in neuropathic pain model mice. It has been thought that Ca^{2+} dynamics at fine astrocytic processes regulate synaptic functions/neuronal excitability. However, its dynamic interaction between neurons and astrocytes is largely unknown. To this end, we took viral introduction of red fluorescent genetically encoded Ca^{2+} indicators (GECI) and green fluorescent GECI into neurons and astrocytes, respectively. We have succeeded to monitor both spontaneous and evoked Ca^{2+} signals simultaneously from neurons and astrocytes in the hippocampus in situ. Enhancement of astrocytic Ca^{2+} signals by selective manipulation of astrocytic receptors altered dendritic Ca^{2+} excitation. The approach described here may provide useful information on bidirectional information processing at synapses.

3-YS-3
Cortical spreading depression: target for the migraine treatment.

Chiho Kudo[1]

[1]Department of Dental Anesthesiology, Osaka University Graduate School of Dentistry

Migraine is an episodic neurological condition which prominent symptom is a recurrent, severe, unilateral pulsating headache, which prevalence is 8.4% in Japan. Clinical characteristics of migraine, in addition to severe headache, include photophobia, phonophobia or autonomic nervous symptoms such as nausea and vomiting. Although migraine is not life threatening, it has a significant impact on migraine patient's quality of life. Cortical spreading depression (CSD) is defined as a transient neuronal and glial depolarization and disruption of membrane ionic gradients that propagates slowly across the cerebral cortex. There is a growing evidence from animal experiments, suggesting that CSD is the electrophysiological event underlying migraine aura and activates the trigeminovascular system and upper central nervous system, resulting in the headache. In addition, the functional MRI performed on patients during migraine with aura attacks revealed a causal role of CSD. These basic and clinical findings suggest that CSD plays a pivotal role in the pathophysiology of migraine.
Here, I review the potential correlation between the migraine pathophysiology and CSD for the knowledge necessary to develop the new therapy for migraine.

3-YS-4

Enhancement of response to nociceptive stimulus in the cerebral cortex of an ectopic pain model of the rat

Satoshi Fujita[1], Kiyofumi Yamamoto[1], Masayuki Kobayashi[1]

[1]Dept. Pharmacol., Nihon Univ. Sch. Dent.

The inferior alveolar nerve (IAN) is a mandibular branch of the trigeminal nerve and innervates to orofacial region. IAN transection (IANX) induces allodynia in the maxillary nerve-projecting region. However, it is not fully understood whether and how the nociceptive information processing in the cerebral cortex is changed by nerve injury. To address this question, we assessed neural activity during nociception in IANX rats using optical imaging and two-photon calcium imaging techniques. Since the dental pulps principally consist of Aδ and C fibers that transmit nociceptive information, we used dental pulp stimulation to investigate the cortical response to nociception. Optical imaging at macroscopic level revealed that cortical excitation induced by the upper molar pulp stimulation was enhanced in 1 week after IANX. Two-photon calcium imaging revealed that hyperexitability of both excitatory and inhibitory neurons. Whole-cell patch-clamp recording in slice preparation revealed inhibitory postsynaptic inputs to pyramidal neurons were decreased in IANX rats. These results suggest that IANX induces enhancement of neural activity during nociceptive information processing, and plastic changes of the local circuits in the cerebral cortex might contribute to the enhancement.