1-JS1-1 Joint Symposium

First-in-Human (FIH) to Proof-of-Concept (PoC) studies in Japan for early access of pharmaceuticals for patients around the world, even at an international pharmaceutical company

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At international pharmaceutical companies and even at some Japanese pharmaceutical companies, FIH to PoC studies are usually conducted outside Japan. However, there are many professional clinical pharmacology (CP) sites in Japan that can conduct FIH studies meticulously, resulting in lower variability of data and decreased noise. This is advantageous to see signals of biomarkers in a relatively small study. A common misunderstanding is that Japan is slow and expensive to conduct clinical studies. This is not true. The regulatory timeline of Japan's first Clinical Trial Notification (CTN) is 30 days, which is the same as opening an Investigational New Drug (IND) in USA. Recent examples showed that Japan CP sites are less expensive than sites in USA. So why are FIH and PoC studies not conducted in Japan? It is because people outside Japan do not realize that there are great CP and PoC sites in Japan, and do not trust the Japan affiliate to conduct these studies. Since I moved to Novartis, I have been leading the Translational Medicine Japan department, which includes pharmacology, toxicology, pharmacokinetics (PK) and operations from Phase 1 to PoC. For early access to pharmaceuticals for patients around the world, we would like to conduct FIH to PoC studies in Japan, even at an international pharmaceutical company.

1-JS1-2 Joint Symposium

Development and induction of the new human study program as an item in pharmacologic exercise for medical students.

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In the medical education, conducting student practice has a significant educational value. Because almost all medical students will administer a drug as a physician after acquired a physician license, pharmacologic exercise is quite important during the medical education. At Showa University, several human study program items that the medical students were actually given a drug and directly experienced pharmacological action with their own body have been installed more than 40 years in the pharmacologic exercise. The development of the new training item resulting in a high education effect is demanded when we think about a change of the education environment in the medical university including diversification of the medical treatment and a problem of the man power of the teacher especially medical doctor staff. Recently we developed the new human study training item using the diuretics and installed in the pharmacologic exercise at the 4th year medical student in Showa University. I will introduce the afferent process in the presentation.

1-JS1-3 Joint Symposium

Pharmacological approach and diagnosis for Alport syndrome

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Alport syndrome is a hereditary glomerular disease caused by mutation in the *COL4A3, COL4A4*, or *COL4A5* gene encoding type IV collagen alpha 3, alpha 4, and alpha 5 chains (alpha 3-alpha 5(IV)), respectively, which are components of the glomerular basement membrane (GBM). The most common mutations are those in *COL4A5*, which comprise more than 80% of AS-associated mutations. Mutant achains cannot form alpha 345(IV) trimer, which leads to abnormal GBM. In current therapeutic approaches for the management of Alport syndrome, inhibitors of the renin angiotensin system (RAS) are typically prescribed. Although early intervention by RAS blockade suppresses the progression of nephritis, patients with Alport syndrome taking RAS inhibitor eventually develop end-stage renal disease. Numerous basic studies have revealed the molecules that are associated with the progression of Alport syndrome. However, candidate drug targets have not been assessed in clinical applications, and a novel therapeutic strategy is urgently needed. We have established collagen alpha 345(IV) heterotrimer formation assay system that is amenable to high throughput screening (HTS) by using split luciferase compliment system (NanoLucTM) (Omachi, et al., Cell Chem. Biol. 2018). The assay provided evidence that compared with wild-type alpha 345(IV) trimer, the heterotrimer with mutant alpha 5(IV) had either intracellular trimerization defect or trimer secretion defect. We have started screening of natural compounds in our original library using alpha 5(IV) G1244D-expressing cellular system, and are trying to find potential candidate compounds to correct the mutant alpha 5(IV)-dependent defect of alpha 345 (IV) trimer secretion. Furthermore, we will also discuss the recent progress on the generation of new Alport mouse models with missense mutations in C57BL/6 and 129 strains that may be usable for future analysis of the in vivo efficacy of our candidate compounds.

1-JS1-4 Joint Symposium

Transporter inhibitors: from target identification and pharmacology to clinical development

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Transporters on the plasma membrane contribute to determining the distribution of compounds in the intra- and extracellular compartments and eventually their disposition in the body. Thus, the drugs that affect the functions of transporters are expected to alter the distribution of compounds in the body and to ameliorate disrupted homeostasis in pathological conditions. In fact, the drugs targeting transporters, such as antidepressants, diuretics and uricosuric agents, have been used clinically. They were, however, developed before the identification of targets. Now, we have a lot of information on transporters in human genome that can be targets of new drug discovery. For example, anti-diabetic drugs have been successfully developed targeting renal Na^+/glucose cotransporter SGLT2. The molecular identification of SGLT2 contributed to the critical optimization of the compounds. We have identified an amino acid transporter LAT1 expressed in cancer cells with high cancer-specificity. Based on the structure-activity relationship analyses, we have developed its inhibitors which are now in the clinical trials. In the lecture, the issues we have experienced in the process of compound developments, pre-clinical studies and bridging toward clinical trials will be summarized, and the importance of basic and clinical pharmacology collaboration will be discussed in terms of academia drug discovery.

1-JS2-1 Joint Symposium

Possible role of microglia in mental disorder-related hearing impairment

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Disrupted processing of auditory information including auditory hallucination is a challenging problem that affects the quality of life of patients with mental disorders. Here we report that microglia, the brain resident immune cells, play a key role in the disruption of auditory information processing in a mouse model of adult temporal lobe epilepsy (TLE). We found that the chemoconvulsant kainic acid (KA)-induced status epilepticus significantly activated microglia in the medial geniculate nucleus (MGN), a brain region which sends ascending projection to the auditory cortex. In the MGN, microglia wrapped the soma of MGN neurons and stripped axosomatic inhibitory synapses to these neurons. The synaptic striping by microglia decreased the inhibitory synapse density, resulting in the elevation of c-fos expression in neurons of the MGN as well as the auditory cortex. Furthermore, after KA-induced prolonged status epilepticus, mice exhibited deficits in an auditory perception test to discriminate whether or not sound stimuli are presented; mice behaved as if the sound stimuli were presented when the stimuli were not actually presented. These results suggest that mice experienced auditory hallucination after KA-induced status epilepticus.

1-JS2-2 Joint Symposium

Pharmacological approach to overcome schizophrenia

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Schizophrenia is a severe mental illness that affects about 1% of the population. However, the exact pathoetiology remains unclear and no effective treatment has been available yet. Rare or de novo copy-number variations (CNVs) are likely the most significant contributors to the pathogenesis of schizophrenia. We recently found novel schizophrenia-associated CNVs including ARHGAP10 which encodes a member of the RhoGAP superfamily. ARHGAP10 mutant mice showed an increase in anxiety level. ARHGAP10 mutant mice also manifested potentiation of hyperlocomotion and discriminative cognitive impairment induced by methamphetamine treatment. Morphological analysis revealed that ARHGAP10 mutant mice showed a decrease in neuronal spine density in the medial prefrontal cortex compared to the wild-type mice. Methamphetamine-induced cognitive impairment in ARHGAP10 mutant mice was ameliorated by the treatment with fasudil in dose-dependent manner. These results suggest that mutations in ARHGAP10 increase the risk of schizophrenia, and ARHGAP10 mutant mouse is a novel animal model of schizophrenia based on copy-number variations. Rho signaling pathway may be a potential therapeutic target to develop novel antipsychotics.

1-JS2-3 Joint Symposium

Chronic stress causes excessive aggression by altering synaptic actin dynamics in the mPFC.

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Behavioral and psychological symptoms of dementia (BPSD) are an integral part of dementia syndrome. In particular, BPSD such as chronic stress induced excessive aggression is known to be more stressful to caregivers than the cognitive and functional problems of the patients with dementia. Therefore, the effective treatment for excessive aggressive behavior is required. There is evidence that functional circuits in the medial prefrontal cortex (mPFC) regulate social cognitive functions including aggressive behaviors. Also, social isolation, one form of chronic stress environment, can lead to the development of excessive aggression. However, the underlying cellular and molecular mechanisms of the mPFC neural network involved in chronic stress environment induced aggression is largely unknown.

To clarify the molecular mechanism of mPFC neuronal network with excessive aggression, we examined aggressive behavior in rat model of chronic social isolation focusing on mPFC synaptic plasticity. We further investigated the relationship between synaptic actin dynamics and AMPARs delivery in spines of mPFC of chronic stressed animals. Here, we show that chronic stress environment changes spines in the mPFC by reducing actin dynamics, leading to the decrease of synaptic AMPA receptor delivery and altered social cognition and aggressive behavior. Our study provides molecular and cellular mechanisms underlying the influence of chronic stress environment on social cognition and aggression.

1-JS2-4 Joint Symposium

Mechanisms underlying the development of mental disorders revealed using novel PET tracer recognizing AMPA receptors

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Glutamate AMPA (alfa-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (AMPARs) play central roles in neuronal functions. However, clinical translation of knowledge on AMPARs accumulated in a number of animal studies has been limited due to the inability to visualize AMPARs in living human brain. Thus, we developed positron emission tomography (PET) tracer for AMPARs based on the compound already known to bind to AMPARs specifically. Using this tracer, we carried out the clinical study to examine the densities of AMPARs in some patients with mental disorders. Some diseases showed the strong correlation between the disease severity and the density of AMPARs. Interestingly we could reproduce the same phenotype of patients in the mouse where the expression levels of AMPARs were changed as seen in these patients with genetic manipulation. This bidirectional approach between animal and clinical researches is promising to delineate the specific brain regions responsible for the development of mental disorders and can contribute to the development of novel drugs and therapies toward mental disorders.

1-JS3-1 Joint Symposium

Parkinson's disease and deep brain stimulation(DBS)

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Parkinson's disease (PD) is a hypokinetic movement disorder characterized by bradykinesia/akinesia, resting tremor and muscle rigidity. These motor symptoms are mainly caused by degeneration of dopaminergic neurons in the substantia nigra. Since 1967, when L-dopa was shown to effective for amelioration of the motor symptoms of PD, dopamine replacement therapy remains the mainstay of medical therapy for PD. On the other hand, stereotaxic surgery for PD was developed in 1948, leading to the findings that targeted destruction of the globus pallidus pars interna (GPi) and the intremedialateral nucleus of thalamus (Vim) represent effective therapies for bradykinesia/akinesia and tremor, respectively. In 1980s, deep brain stimulation (DBS), in which electrode is implanted into deep structures of the brain, was developed and shown to be effective as well as surgical destruction. In 90s, the subthalamic nucleus was demonstrated to be a novel target for DBS. Currently STN-DBS and GPi-DBS constitute standard therapies for patients with advanced PD, whose motor complications associated with long-time L-dopa treatment are not properly managed. For advanced PD, on the other hand, other devise-aided therapies(DAT) including L-dopa/carbidopa intestinal gel could be alternative options. The current indication and future prospect of DBS in the PD therapy will be discussed.

1-JS3-2 Joint Symposium

Deep Brain Stimulation for Parkinson's Disease

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There is a long history of surgical treatment for Parkinson's disease (PD). Formerly, ablative stereotactic procedures such as thalamotomy or pallidotomy were performed. Currently, deep brain stimulation (DBS) is the most promising surgical treatment option for patients with medically refractory PD. DBS modulates neurological function of the target region using implanted medical devices to deliver electrical stimulation to the brain. Currently, the most common target of DBS for PD is the subthalamic nucleus (STN). The appropriate surgical candidate for STN-DBS suffers from motor complications from levodopa such as fluctuations and dyskinesia. STN-DBS significantly improves motor function in the medication-off state, motor fluctuations and dyskinesia with reduction of dopaminergic medication. Long-term outcomes are favorable for cardinal motor symptoms such as tremor, rigidity, and bradykinesia. However, refractory axial symptoms concerning speech, swallowing, gait and postural stability gradually deteriorated with progression of disease. New strategy to treat these axial symptoms is the future subject.

1-JS3-3 Joint Symposium

DBS - from a viewpoint of system neurophysiologist

Atsushi Nambu

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Deep brain stimulation (DBS) that applies electrical stimulation to deep brain structures is an effective therapy for movement disorders such as Parkinson's disease (PD), but its detailed mechanisms still remain to be elucidated. By recording neuronal activity in PD model animals, we found that PD symptoms are caused by decreased information flow through the *direct* pathway and increased information flow through the *indirect* pathway in the basal ganglia, and that DBS blocks information flow at the stimulating site.

To improve the methods of DBS and expand its application, the following studies are necessary: 1) changes in information flow through the affected brain regions in various neurological disorders; 2) simulation of DBS; 3) differences in the mechanisms between classical stereotactic surgery and modern DBS. For that purpose, I would like to propose the followings: 1) participation of increased number of basic researchers who study pathophysiology of neurological disorders, clinicians who are interested in basic neuroscience, and engineers who understand biology; 2) cooperation between neurologists and neurosurgeons in the clinical practice of DBS; 3) participation of psychiatrists to expand the application of DBS to psychotic symptoms; 4) partnership with medical industries to improve DBS devices.

1-JS3-4 Joint Symposium

Medical student training program for medical research - programs and efforts in the University of Tokyo

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Multiple evidences show the clear tendency of less medical students selecting the careers of basic science researchers. There are multiple factors that influence the behavior of medical students for their choice of future careers. It is discussed that the following factors have major impacts. (1) less stable financial condition of basic medical researchers, (2) competitive situation of obtaining academic positions, (3) general trends in both the government and the society to emphasize application of scientific findings more than bottom-up strategies of basic medical sciences, and (4) shrinkage of research budget open to basic medical research. In my presentation, I will introduce the programs and efforts in the University of Tokyo to facilitate "research mind" of the medical students and help them select the best career path in the stage of postgraduate training in either basic research or clinical practice. We evaluate that the programs in the University of Tokyo have developed steadily with success in promotion of young basic researchers, which may be informative for other medical schools.

1-JS3-5 Joint Symposium

DBS: From the point of view of glial functions

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Glial dysfunction is a cause of brain diseases including neuropathic pain. We previously demonstrated that in the primary somatosensory cortex (S1) of neuropathic pain model mice, astrocytes become activated, release synaptogenic molecules such as thrombospondin, and cause uncontrolled synapse-formation, thereby leading to misconnection of innocuous and nocuous networks. This misconnection in the S1 cortical networks is a cause of neuropathic pain allodynia. Thus, an appropriate control of astrocytes can be a major therapeutic strategy. Deep brain stimulation (DBS) is frequently used for the treatment of neurodegenerative diseases such as PD, psychiatric diseases, and neuropathic pain. Although its therapeutic effects are recognized, the molecular mechanism is not well understood. Recently, DBS is shown to affect glial cell functions especially astrocytic Ca^{2+} signals and gliotransmission, which may be involved in its therapeutic effect. Thus, glial cells could be a potential therapeutic target for these diseases. When there is an effective treatment such as DBS, the etiology can be elucidated by thoroughly verifying its action. It is important to link such a clinical top-down research with basic bottom-up research, for which pharmacology plays a central role as an interface. In this symposium, I will also discuss how to promote young scientists by sharing such an attractive and dynamic collaboration of basic and clinical researches.