An Innovative Approach to the Discovery of DSP-1181: Contributions of Artificial Intelligence, Optogenetic Technology, and Translational Biomarkers to CNS Drug Discovery

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DSP-1181 is a novel compound which was discovered by Sumitomo Dainippon Pharma Co., Ltd. using AI (Artificial Intelligence) technology of Exscientia Ltd. It has garnered attention for completing drug discovery research in less than 12 months, compared to the industry average of four and a half years. DSP-1181 has been developed as an orally active agent for OCD (Obsessive Compulsive Disorder), and its Phase 1 study was initiated in Japan in 2020. Here, we introduce an innovative approach to the drug discovery of DSP-1181 utilizing AI, optogenetic technology, and translational biomarkers.

Introduction

Sumitomo Dainippon Pharma Co., Ltd. (hereinafter called our company) is continuously trying to discover excellent drugs, positioning psychiatric and neurological disorders as one of the priority fields. Issues in drug discovery for psychiatric and neurological disorders include the following: there are still many uncertainties in clinical conditions; there is few disease model mimicking human pathophysiology completely; the probability for success in development is generally low; and especially in psychiatric disorders, the patient population is not uniform, and high placebo effects[*1] are observed in clinical studies. From the viewpoints of promoting the efficiency of research and development and improving the probability for success in development, our company is actively employing studies that use digital technology, those that focus on abnormalities in neural circuits and genes rather than behavioral phenotypes in patients with a subjective diagnosis based on symptomatology, and translational biomarker research bridging the gap between nonclinical (in rodents and non-human primates) and clinical data (in healthy adults and patients). In addition to in-house studies, our company is aiming to engage in studies incorporating the latest technologies from every direction, such as technology introduction and joint studies with venture companies and academia.

Among them, DSP-1181 has garnered attention for completing drug discovery research in less than 12 months, compared to the industry average of four and a half years[1]. DSP-1181 is a small molecular compound discovered by our company using the artificial intelligence (AI) technology of the British company

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*1 Placebo effect: A phenomenon in which some individuals experience side effects or improvement in symptoms after they take an inactive substance (placebo). Psychological factors are thought to contribute to placebo effects to a large extent.

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Exscientia Ltd. (hereinafter called Exscientia). It is a serotonin 5-HT$_{1A}$ receptor agonist*2 characterized by the potent full agonist activity, whereas all of the 5-HT$_{1A}$ receptor agonists launched as anxiolytics are partial agonists. DSP-1181 has been developed as a drug candidate for obsessive compulsive disorder (OCD), and its Phase 1 study was initiated in Japan in 2020.

OCD is a psychiatric disorder presenting obsessions (recurrent and persistent thoughts, images, or urges), compulsions (repetitive behaviors or mental acts), or both, which are time consuming (take more than 1 hour/day) or cause social and occupational disorders to decrease the quality of life[2]. Although the first-line drug treatment for patients with OCD is selective serotonin reuptake inhibitor (SSRI) antidepressants, they are not effective in approximately 40% of patients with OCD[3] and require caution about adverse drug reactions including gastrointestinal symptoms (such as nausea and diarrhea) and sexual dysfunction. Atypical antipsychotics are used in combination with SSRIs, although they are off-label use and require caution about adverse drug reactions, such as extrapyramidal symptoms, anticholinergic effects, weight gain, and hyperglycemia. Drug treatments for patients with OCD are inadequate, and there are needs for highly effective and safe drugs.

In this article, with the case of DSP-1181 as an example, we introduce an approach to drug discovery focusing on leading-edge AI, optogenetic technology, and translational biomarkers.

Efforts to early discover candidate compounds for development —Drug discovery utilizing AI—

1. Exscientia AI platform for drug discovery

According to the survey by Jack W. Scannell *et al.*[4], the annual number of new drugs approved by the Food and Drug Administration (FDA) in the United States (US) per billion dollars spent in research and development decreased by half every 9 years in the period between 1950 and 2010. A decrease in the productivity of

research and development in pharmaceutical industry has been a major issue[4]. Some individuals involved in drug development even call it Eroom's Law, which is the exact opposite of Moore's Law (the number of transistors on a microchip doubles every 18 months). The major causes include the following: the number of new drugs is not increased enough for the investment despite an increase in the research and development cost; the development of drugs takes a longer time with increasing cost because of tightening regulations, *etc.*; and the average values of products are decreasing[4,5]. Because the trend in research and development has shifted from the blockbuster model to personalized medicine, it is essential for pharmaceutical companies to enhance the value of each product by improving their expertise in specific areas and to streamline their research and development. Due to an advance in deep learning in the 2010s, the third AI boom has started. Currently, AI is actively used in various areas, such as healthcare, manufacturing, agriculture, delivery, translation, and automated driving. It is not too much to say that not a day passes without our seeing the word "AI." In this regard, drug discovery research is no exception. Efforts have been made to streamline research by using AI, and there are many companies that provide such services. Our company has been promoting the efficiency of the research process by utilizing in-house and external AI/*in silico**3 technologies. As part of the activities, we conducted a joint study with Exscientia, a pioneer in AI drug discovery, for nearly 3.5 years in the period between 2014 and 2017. There are various approaches to AI drug discovery, and we briefly describe the AI drug discovery platform used by Exscientia in the joint study.

The Exscientia AI platform for drug discovery achieves high productivity when the AI and human capability cooperate with and complement each other. Our company as the human capability expected the following 2 technologies of Exscientia. One is the technology to automatically generate the structures of compounds. On a computer, it generates the chemical structures of compounds from the starting compound

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*2 Agonist: A drug that binds to receptors and functions the same way as biological molecules. According to the intensity of activity, agonists are classified into 2 categories, namely, full agonists and partial agonists. The action of the former is equal to or stronger than that of biological molecules, whereas the latter acts more weakly and sometimes inhibits the function of biological molecules.

*3 *In silico*: It means "in or on a computer (silicon chip)." It was coined as an allusion to the phrases of *in vivo* (within the living) and *in vitro* (in test tubes). It is a technology to conduct virtual experiments on a computer to predict the pharmacological effect on the target proteins and pharmacokinetic profiles of a compound.

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according to a certain rule. Those compounds are generated considering the synthetic feasibility and novelty (that it is a novel compound unknown worldwide). The other is a knowledge-based AI predictive model. By applying this predictive model to the chemical structure generated on a computer, we can predict the targeted pharmacological activity, toxicological effects on the targets, and pharmacokinetic profiles including metabolic stability, membrane permeability, and brain penetration. The combination of these 2 technologies enables us to predict the pharmacological activities and pharmacokinetic profiles of an enormous number of virtual compounds generated by the automatic structure generation. By repeating this cycle on a computer, we can propose a compound that is likely to have the intended profiles (**Fig. 1**).

For details in this AI drug discovery platform of Exscientia, see the article, "Automated design of ligands to polypharmacological profiles," in the British science journal Nature in 2012[6].

2. Exploratory research

We completed the discovery of DSP-1181 in less than 12 months after the start of exploratory research, making full use of AI (this is the period until a compound with the targeted profiles has been discovered, excluding the safety evaluation). It is under investigation in the Phase 1 study. In this article, we do not disclose many matters related to the drug discovery research, including its chemical structure and structure–activity relationship, for keeping a competitive advantage of our company. We describe below how we discovered DSP-1181 in the exploratory research, although limited.

In the joint study with Exscientia for nearly 3.5 years, we implemented several projects to discover therapeutic drugs against psychiatric disorders that targeted monoamine[*4] G-protein-coupled receptors (GPCR)[*5], such as serotonin receptors and dopamine receptors. We have discovered several (candidate) compounds for development so far. DSP-1181 is a compound that was discovered in the project intended to discover a drug with the 5-HT1A receptor agonist activity as treatment against anxiety-related disorder. Key points in this early discovery of DSP-1181 are as follows. First, we were greatly surprised at Exscientia's high AI technological capability for drug discovery when we started this project. Generally, it is not easy to design the compounds that have both the targeted action on the target proteins and desirable pharmacokinetic profiles as treatment against psychiatric disorder at the early phase of exploratory research. When we synthesized and evaluated the compounds that Exscientia proposed at the beginning, they showed the activity on the target proteins and good pharmacokinetic profiles, so we obtained a lead compound early in the project. Better compounds are designed by evaluating a synthesized compound in an *in vitro* study and feeding back the data on its activity into Exscientia's AI predictive model to improve the model. We repeated this cycle to obtain the more potent activity on the target proteins. After the project progressed steadily, we met an obstacle approximately 3 months after the start. It became difficult to strengthen the agonistic activity on 5-HT1A receptors. The compounds synthesized by then had high binding activities to 5-HT1A receptors but less potent agonistic activities. We performed the structure generation based on the matched molecular pairs analysis (MMPA)[7] that was intended to enhance the agonistic activity, and as a
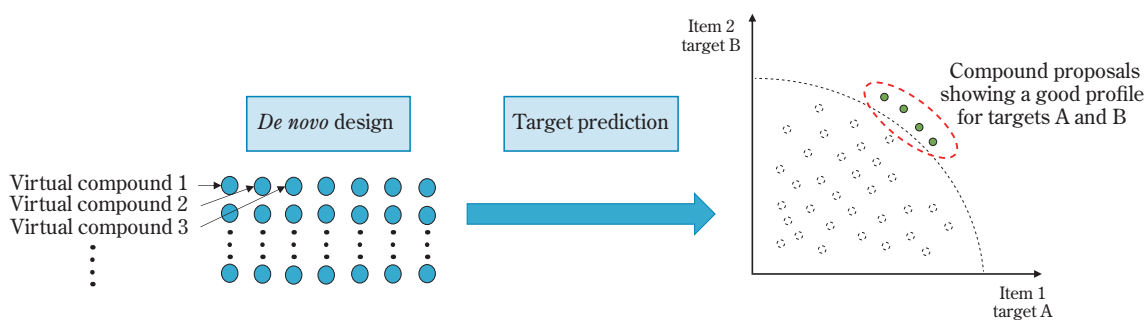
*4 Monoamine: The general term for neurotransmitters, such as serotonin and dopamine.
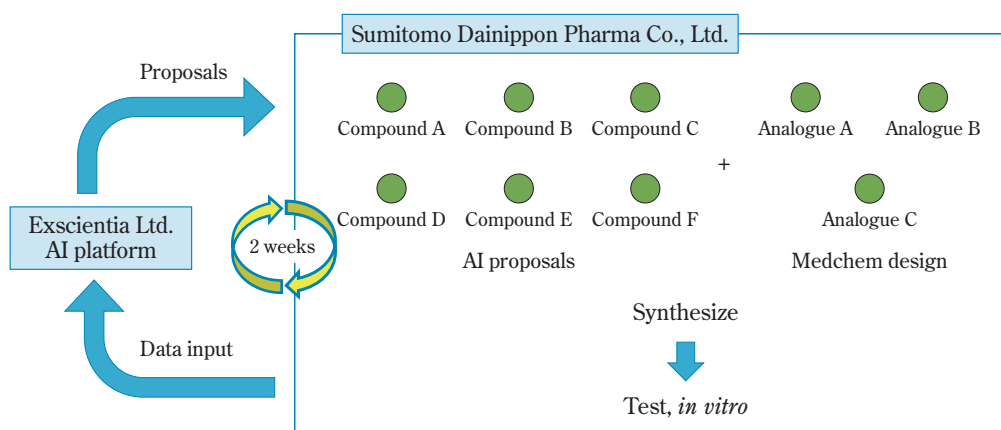*5 GPCR: A form of receptors in the living.

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Fig. 2　2-week cycle

result, we overcame this obstacle resulting in the further progress in the research. In addition to the automatic and comprehensive structure generation, we recognized the effectiveness of complementation based on a different type of structure generation, to solve problems in some endpoints. This experience led to the structure proposal (design) from drug discovery chemists mentioned below.

Another cause for the early discovery of DSP-1181 was the "2-week cycle." At short intervals of 2 weeks, we repeated the cycle in which the company's chemistry team synthesized the compounds proposed by Exscientia, the pharmacology team assessed the compounds, and our company shared the data on their activities with Exscientia (**Fig. 2**). This required a high ability to promptly synthesize the proposed compounds and the technical ability to perform *in vitro* assays accurately and rapidly. DSP-1181 was the 350th compound synthesized after the start of the project. We synthesized and tested as many as 350 compounds in less than 1 year because we promptly implemented this "2-week cycle."

The following is also very important. Our company synthesized not only the compounds proposed by Exscientia but also some analogues at the same time. Using the intermediates needed to synthesize the proposed compounds, drug discovery chemists in our company designed and synthesized the compounds presumed to show meaningful pharmacological data and inputted the data into Exscientia's predictive model. They included the compounds that gave an important structure–activity relationship for optimizing the structures of compounds, which further accelerated the drug discovery cycle. The combination of Exscientia's high AI technology for drug discovery and the experience of drug discovery chemists in our company enabled us to discover DSP-1181, a full agonist with a potent activity on 5-HT1A receptors in contrast to the existing 5-HT1A receptor agonists, such as buspirone and tandospirone (our company's Sediel), in a short period.

Efforts to improve the probability for success in clinical development
—Verification of nonclinical efficacy focusing on neural circuits—

1. Trends in the research and development of drugs against psychiatric disorders

In the current treatment for patients with psychiatric disorders, there are still unmet medical needs[*6] to be met by a breakthrough in the drug industry's research and development of new drugs. However, some large pharmaceutical companies have decided to withdraw from the research and development in this area because of the low probability for success in the development of drugs against psychiatric disorders[8]. The causes for the low probability for success include an unknown whole picture of the pathophysiology, few appropriate nonclinical tests and animal models, and the high heterogeneity of patients with the same diagnosis[9),10)].

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*6 Unmet medical needs: Requests and demands in medical practice including patients for treatment against the diseases and symptoms for which the existing therapies are ineffective.

The high heterogeneity of patients with a psychiatric disorder indicates that patients with the same diagnosis vary more widely in symptoms and causes of disorder than patients with other diseases. In a number of large-scale clinical studies in the patients recruited under the same diagnosis, the efficacy of a drug was not established by a statistically significant difference because there were both responders and non-responders at the same time[11]. One of the causes for the heterogeneity of patients is few biological indices to distinguish the disorder from other diseases for definitive diagnosis, such as blood test and imaging. Vigorous effects have been made to improve objective indices for a deeper understanding of psychiatric disorders. One example is the Research Domain Criteria (RDoC), a research framework promoted by the US National Institute of Mental Health (NIMH). The RDoC is an effort to compare biological indices with abnormal neural circuits in the functional domains (positive/negative emotional valences, cognition, sociality, and arousal) that may contribute to the disorder, to elucidate the abnormalities in genes, molecules, cells, neural circuits, *etc.* that are common to the functional domains (symptoms)[12].

The efforts focusing on the abnormal neural circuits, which are more pathophysiological, may reduce the heterogeneity of patients, leading to more effective treatment strategies. For example, it is suggested that the treatment effect can be predicted in a certain biotype of patients with depression when they are classified into 4 biotypes according to the functional connectivity between brain areas[13]. Such investigations are becoming active to identify the pathology in the neural circuits that are involved in the symptoms of psychiatric disorders, and to enhance the understanding of the pathophysiology based on objective indices including neural circuits, by classifying patients according to their symptoms rather than their diagnoses. We also believe that it is important to reflect this strategy in the approach to the research and development of drugs.

Abnormal neural circuits in psychiatric disorders have been gradually revealed with advances in brain imaging technologies. It has been reported that an abnormality in neural circuits contributing to OCD is an increase in the functional connectivity between the cerebral cortex and the striatum, which is associated with the hyperactivity of the anterior cingulate cortex and orbitofrontal cortex[14),15)]. Symptoms and abnormal neural circuits in OCD are obviously related to the 5-HT nervous system because SSRIs have been approved as drugs for OCD treatment, for example. Therefore, 5-HT$_{1A}$ receptors, a subtype of 5-HT receptors, are a preferable target, and DSP-1181 is a promising treatment against OCD.

2. Utilization of innovative technologies for neural circuit manipulation in drug discovery research

Until now, the marble-burying behavior in mice has been employed as a typical nonclinical animal model to predict the efficacy of a drug against OCD pathology[16]. This test uses the aversive behavior (compulsive-like behavior) of mice in response to glass marbles and assesses the behavior of burying marbles placed in a cage within a certain time. In addition to the unknown construct validity*7 of this model, its predictive validity*8 is also questionable because there is a discrepancy between the test results and the clinical efficacy of drugs; for example, a single dose of an SSRI showed efficacy. As mentioned above, a cause for a low probability for success in drug discovery is few appropriate disease models that can predict clinical efficacy. We tried to create a new OCD model by reproducing the abnormal neural circuit considered to reflect better clinical pathophysiology, using technology for neural circuit manipulation, which has achieved a remarkable advance in recent years.

A representative technology for neural circuit manipulation is optogenetic technology. This technology has caused a paradigm shift in neuroscience to allow us to reversibly regulate a activity of specific neuronal population in a free-moving animal with a high time resolution (on the millisecond timescale). The key molecule in this technology is a photoreceptor protein, channelrhodopsin (ChR). ChR is a subtype of rhodopsin (a photoreceptor protein), and in 2002, Peter Hegemann *et al.* reported that this molecule allows cations to pass into the cells when it is exposed to light[17]. Karl Deisseroth *et al.* applied this molecule to neuroscience and reported for the first time in the world that an

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*7 Construct validity: A validity that refers to whether behaviors and neurological changes in an animal disease model are consistent with clinical presentations.

*8 Predictive validity: A validity that refers to whether a therapeutic drug against a disease is effective in an animal disease model.

action potential was generated in the neuron by exposing ChR expressed in cultured cells to light[18]. This discovery is innovative because the exposure to light can change the action potential only in the cell expressing ChR, which enables us to regulate the action potential in the cells of a specific brain area *in vivo*. Deisseroth's discovery has led to a further innovative technology of irradiating a specific brain area locally with light by expressing ChR in the living brain with a recombinant adeno-associated virus. Optogenetic technology enables us to analyze the relationship between neural circuits and their functions locally to understand the complex neural circuit networks in the brain.

With optogenetic technology[19], we tried to manipulate the circuit between the orbitofrontal cortex (OFC) and the ventromedial striatum (VMS) in the brain of living mice. This is reported as a responsible neural circuit for OCD pathology. In the OFC area in anesthetized mice, we injected recombinant adeno-associated viruses, rAAV-DJ/8(mCamKIIα)-mCherry or rAAV-DJ/8(mCamKIIα)ChR2(H134R)-mCherry. After a certain period for recovery, we implanted an optical fiber in the VMS area and evaluated grooming behavior in mice when the VMS area was exposed to light (**Fig. 3**). Before exposure to light (Pre), no difference was detected between the control group and the ChR group. By light stimulation (Stim), the grooming time was markedly increased in the ChR group, and the effect disappeared an hour after light stimulation (**Fig. 4**). After evaluating behaviors, we isolated the brains and, with fluorescence labelling, evaluated neural hyperactivity in the VMS area due to virus injection and light stimulation locally in the OFC area. As a result, we confirmed that we had manipulated the intended neural circuit in the prepared animals. The above results demonstrated that the OCD-like behavior (grooming behavior) was increased by stimulating and excessively exciting the OFC–VMS neural circuit specifically with optogenetic technology. It can be said that this is a new animal model of the OCD pathology with a good construct validity, which has not been confirmed in the conventional animal models of OCD. In this mice model of OCD, we evaluated the actions of DSP-1181 and an SSRI. The SSRI is used as a drug against OCD in Europe, and we used it to investigate the predictive validity. After light stimulation and the administration of drugs, grooming behavior was evaluated. The data are shown on the first day of administration and after administration for 5 consecutive days (**Fig. 5**). Grooming
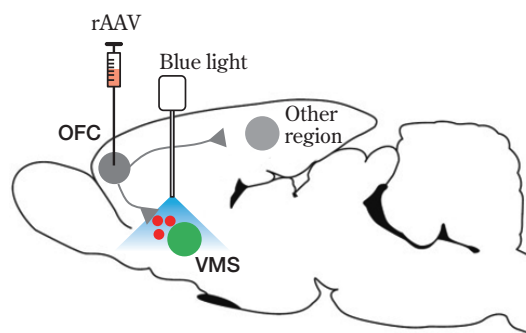

Fig. 3 Schematic representation of neural circuits and experimental method in the brain of a rodent
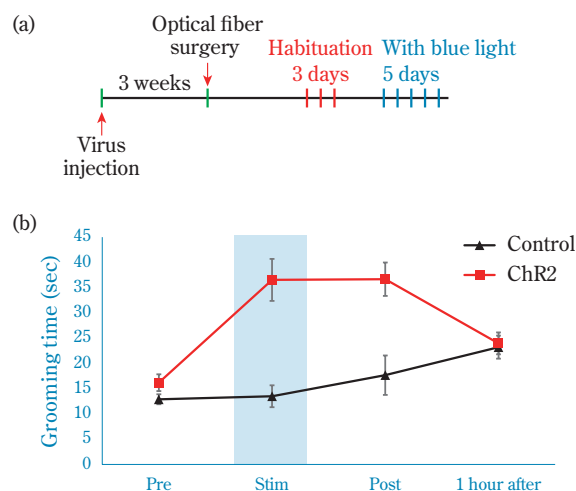

Fig. 4 (a) Experimental schedule and (b) Effect of OFC-VMS hyperactivation on grooming behavior in mice
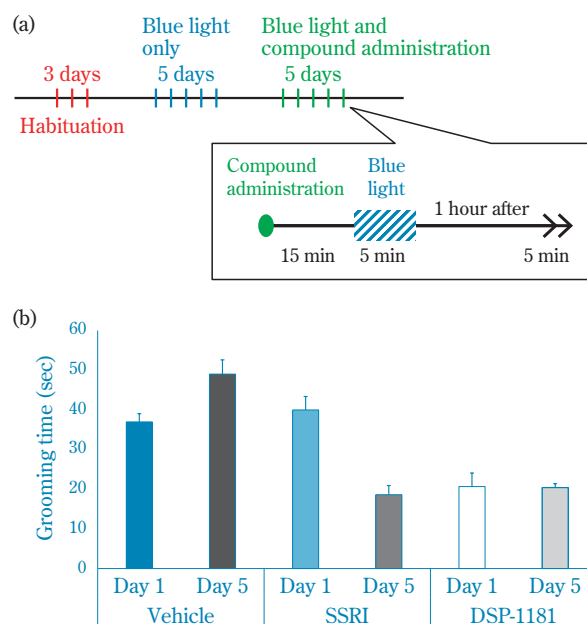

Fig. 5 (a) Experimental schedule and (b) Effect of DSP-1181 and SSRI on abnormal grooming after blue light stimulation

behavior after 5-day administration was decreased in all treatment groups when compared with the vehicle group, whereas it was decreased only in the DSP-1181 group on the first day of administration. These results suggest that DSP-1181 has an early onset of the therapeutic effect on OCD, which may satisfy an unmet medical need in clinical practice because it takes a few weeks to obtain a desired effect from SSRIs. It has been reported that 5-HT1A receptors are expressed at the dorsal raphe nucleus, which 5-HT neurons arise from and SSRIs act on[20]. The early onset of the therapeutic effect of DSP-1181 may be caused by the activation of 5-HT neurons at the dorsal raphe nucleus due to the receptor internalization induced by strongly stimulating receptors.

Approaches to seamless migration from nonclinical to clinical studies

1. Importance of translational research and pupillary change as a biomarker

Translational research is a "bridging research" between nonclinical and clinical studies. Its promotion aims to improve the probability for success in the research and development of new drugs. With regard to what is important for pharmaceutical companies to promote translational research, Pfizer, one of the world's leading pharmaceutical companies, published a thought-provoking report. The report indicated that the probability to obtain the proof of concept (PoC)*9 was more than 85% in the clinical studies in which the 3 pillars (the exposure to the target site, binding, and expression of the function) of a compound were confirmed and was higher than in the studies in which only 2 or less pillars were confirmed[21]. AstraZeneca reported the analysis on the projects that were previously discontinued: the efficacy was insufficient in 88% of the projects in the later stage of development, partly because there was no biomarker for efficacy. Based on those results, AstraZeneca proposed the 5 right framework comprising 5 viewpoints (target molecule,

exposure, safety, patient population, and commercial potential) as the criteria for projects[22]. With these backgrounds, we have established the policy that we should emphasize the biomarker strategy based on objective approaches that can be translated in drug discovery for psychiatric disorders to improve the probability for success in drug discovery. Several approaches including positron emission tomography (PET)*10 and functional magnetic resonance imaging (fMRI)*11 are used to confirm the 3 pillars in the brain. We assessed the action on the pupil as an important translational biomarker because the action to constrict the pupil was reported in multiple drugs whose mechanism of action was the 5-HT1A receptor agonist activity[23),24)].

Pupillary dilation and constriction occur when noradrenaline or acetylcholine regulates the dilator pupillae muscle or sphincter pupillae muscle. For pupillary constriction, it is thought that a 5-HT1A receptor agonist acts on the Edinger–Westphal nucleus (accessory oculomotor nucleus) of the midbrain to constrict the sphincter pupillae muscle via the oculomotor nerve, which is parasympathetic[25]. Pupillary changes depend on the central nervous system function and can be an indicator for the exposure to a drug in the brain (the target area). We tried to establish the nonclinical evaluation that focused on the action to constrict the pupil as a translational biomarker for DSP-1181. It was already reported that 5-HT1A receptor agonists induced pupillary dilation in a nonclinical study in rodents[26]. We considered that the difference in the vector of the action on the pupil may be caused by the species difference in the mechanism of action on the pupil based on the 5-HT1A receptor agonist activity. We started to establish the test system in more human-like non-human primates.

Common marmosets (*Callithrix jacchus*), which originally lived in South America, are a type of New World monkeys and a non-human primate belonging to Cebidae. Because marmosets are small monkeys with a body weight of 300 to 400 g, they can be handled more easily in experiments than macaque

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*9 PoC: To scientifically demonstrate the hypothesis that a development compound has a therapeutic effect on the target disease or condition.

*10 PET: A tomographic imaging of tissues using tracers that emit positrons. When there is a tracer that binds to the receptor to be evaluated, the receptor occupancy of a drug expected to bind to the receptor can be assessed in the brain. The action of a drug on neural activities can be assessed with glucose metabolism.

*11 fMRI: An imaging technique with the cerebral blood flow in the brain that increases and decreases depending on neural activities. With this technique, we can evaluate changes in neuronal connections in the brain area on which a drug acts and between areas.

monkeys. Their reproductive potential is high because marmosets commonly give birth to twins and can give birth twice a year. They have more human-like characteristics than rodents, including the structure of the brain, biological rhythm, high sociality, and verbal communication. Vigorous efforts are being made to use marmosets as laboratory animals for neuroscience[27]. In addition, marmosets are preferable as laboratory animals because their visual function is similar to that of humans. We have established the original system for monitoring eye gaze, eyeblink, and pupil size when visual stimuli are presented to conscious marmosets and have utilized it to evaluate the action of a candidate compound for a new drug. We use trained marmosets in experiments under the environment where the stress from experimental operations is eliminated as much as possible, including a special monkey chair, an automatic feeder that gives rewards, and a soundproof chamber that eliminates the effects of the external environment. With this system, we evaluated the action of a 5-HT1A receptor agonist, buspirone, as a comparator on the pupil. A statistically significant action to constrict the pupil was observed in the buspirone group compared with the vehicle group. We also confirmed that this action was canceled by the pretreatment of WAY-100635, a 5-HT1A receptor antagonist[28]. When DSP-1181 was administered, the action to constrict the pupil was observed in a dose-dependent manner and was canceled by the pretreatment of WAY-100635, as with buspirone (**Fig. 6**). Thus, the pupillary constriction in marmosets after the administration of DSP-1181 was based on the 5-HT1A receptor agonist activity. By establishing the visual function assessment in marmosets, we had the results that supported the appropriateness of the pupillary assessment as a translational biomarker bridging the gap between humans
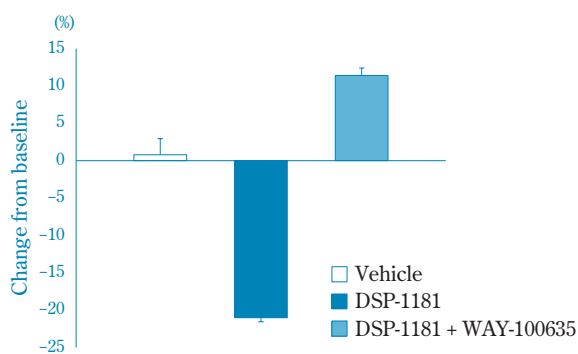
and rodents with respect to the 5-HT1A receptor agonist activity. This advanced approach that focused on translational research has seamlessly led to the first-in-human study of DSP-1181.

2. The first-in-human study in Japan

A first-in-human study is a clinical study in which the safety and pharmacokinetics of a compound are evaluated when it is administered in humans for the first time. In the early stage of the clinical development (such as the first-in-human study) of a compound for patients with psychiatric disorders, pharmacodynamic data, such as translational biomarkers, are often evaluated as indices to early investigate whether the compound acts on the target area in the brain. While we were accumulating nonclinical data on DSP-1181 in the aim of conducting the first-in-human study, the key point to determine the potential of DSP-1181 early and reliably was the feasibility of measuring the pupil diameter in the first-in-human study in healthy adults. Changes in the pupil diameter due to the administration of a drug are very small (nearly 0.3 to several millimeters)[23]–[25]. The adult pupil diameter is changed in the range of nearly 1.5 to 8 mm due to the illuminance in the environment, the autonomic nervous activity, drugs, alcohol, foods and drinks for pleasure, smoking, *etc.*, and it always fluctuates sinusoidally, which is called hippus[29],[30]. In addition, it was necessary to appropriately eliminate measurement artifacts, such as eye blinks, during the measurement of the pupil diameter.

For the development compounds discovered by our company, the first-in-human studies in healthy adults have been shifted primarily to the US from Japan and Europe since the acquisition of Sepracor Inc. (currently Sunovion Pharmaceuticals Inc.). While investigating the feasibility of measuring the pupil diameter, however, we found that the techniques to measure a subtle and fine change (nearly 0.3 to 1 mm) in the pupil diameter in healthy adults were studied also in Japan and Europe. We considered that the measurement of the pupil diameter in the first-in-human study of DSP-1181, which was discovered in Japan, should be performed with a Japanese medical device in a Phase 1 site in Japan, and we made efforts to conduct the study in cooperation with medical professionals. After the clinical research to optimize the conditions for measuring and analyzing pupil diameters, we conducted the first-in-human study of DSP-1181 in Japan.

Fig. 6 Effect of DSP-1181 on the pupil area in marmosets

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Conclusion

In this article, we described the discovery research of DSP-1181, specifically, the application of AI to drug discovery, the use of the OCD animal model with a good construct validity based on optogenetic technology, and translational biomarker research bridging the gap between nonclinical and clinical data, as an example of drug discovery approaches to streamlining research and development and improving the probability for success in psychiatric and neurological areas. Similar to the development of DSP-1181, we have discovered (candidate) compounds for development in a short period by applying the external AI technology to drug discovery research and have streamlined drug discovery research by implementing in-house AI/*in silico* technology in various projects. For the nonclinical models focusing on neural circuits, we have established various models of psychiatric disorders by applying the technology of designer receptors exclusively activated by designer drugs (DREADDs), which can manipulate the activation/inactivation of a specific neural circuit, in addition to optogenetic technology. We are also actively using various imaging technologies to evaluate the actions of compounds on neural circuits in the brain and are continuing the challenge to improve the understanding of neural circuits from many sides. Further, we are promoting translational research by using various technologies (such as electroencephalography during awaking, sleep structure assessment, PET, and fMRI as well as visual function assessment) as biomarkers in drug discovery. With the combination of the above efforts, we discovered as many as 7 candidate compounds for development in FY 2020, which was more than ever before. Currently, we are preparing their first-in-human studies.

Finally, we would like to briefly describe the contribution of the research project system[31] to the drug discovery approach for DSP-1181. The research project system is an in-house system that has been introduced to accelerate the discovery of new innovative drugs in our company when the name of Research Headquarters was changed to Research Division in October 2017. This system is based on the following thought: When a dedicated research project leader leads the research consistently from the early stage until the late stage, his/her enthusiasm is transmitted to other project members and promotes the discovery of candidate compounds for development, and the process results in the confidence of researchers and human resource development. As mentioned in the previous chapter, one of the key points in the DSP-1181 project was to bridge the gap between non-human primates and healthy adults with respect to the miotic action. Because the research project leader consistently led the project from the stage of research until the early stage of development, we succeeded at the clinical research for the measurement of the pupil diameter in Japan and the first-in-human study.

As described above, our company is making efforts to streamline research and development and to improve the probability for success by applying the latest technologies to drug discovery research and continuing translational research. Although drug discovery in the psychiatric and neurological area, which our company is focusing on, is challenging, our company has achievements and know-how because it has developed many products for a long period. We will continue to contribute to patients and healthcare by discovering new drugs based on novel technologies in the psychiatric and neurological area with high unmet medical needs.

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