Outstanding Drugs Developed in Japan

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1 Nivolumab (OPDIVO®)

Nivolumab (product name: Opdivo) is referred to as an immune checkpoint inhibitor. Unlike many antineoplastic drugs, it does not act directly on cancer cells. Its immune checkpoint mechanism inhibits the excessive effects of immune responses, and plays a role in stopping immune responses in order to prevent damage to normal cells. This effect was originally found with respect to programmed cell death-1 (PD-1), which was discovered by the Honjo Laboratory at Kyoto University in 1992. The function was unclear at that time, but in a collaborative study between Kyoto University and the Genetics Institute in the US in 2000, programmed cell death 1 ligand 1 (PD-L1) and 2 (PD-L2) were discovered and found to bind specifically to PD-1.

Cancer cells produced in vivo should be ideally eliminated by killer T cells. However, cancer cells express PD-L1 and PD-L2, which bind to PD-1 on T cells and inhibit T cell action, which interferes with removal of cancer cells by the immune system. Therefore, if the PD-1/PD-L1 interaction can be inhibited, immunocytes may be able to attack cancer cells again. The Honjo Laboratory showed that administration of an anti-PD-1 antibody markedly increased anticancer effects in mice, including effects such as inhibition of metastasis of a transplanted tumor. Based on this background, nivolumab was approved by the US Food and Drug Administration (FDA) in 2006 as a new human anti-PD-1 antibody for research use. A clinical study was initiated in the same year in the US. In clinical trials in the US, the drug was administered to treat solid cancers such as non-small cell lung cancer, prostate cancer, colorectal cancer, renal cell carcinoma, and malignant melanoma, and it is found to be efficacious against all these cancer types. In malignant melanoma and renal cell carcinoma, the response rate was close to 30%. The results were published in The New England Journal of Medicine in 2012, and the efficacy was highlighted in an editorial. Cancer immunotherapy using antibodies was selected as Breakthrough of the Year in 2013 by Science magazine, and is currently attracting increased attention.

Therefore, nivolumab was approved as 'Opdivo' for the treatment of malignant melanoma in July 2014 in Japan—the first such approval worldwide—and was launched in September 2014. At present, one in two Japanese individuals develop cancer and one in three deaths are due to cancer. Therefore, development of an anticancer drug with a novel pharmacological action, such as nivolumab, may have great significance in cancer treatment. It is hoped that such developments will progress further and advance medical care.

2 Favipiravir (AVIGAN®)

Tsuyoshi Hayashi and Yumiko Imai

Laboratory of the Regulation for Intractable Infectious Diseases, National Institute of Biomedical Innovation, Health and Nutrition

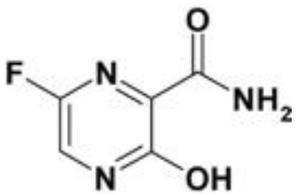

Fig. 1. Structure of Favipiravir (T-705) (Furuta et al. Proc Jpn Acad Ser B Phys Biol Sci. 2017; 93: 449-463).

In 2002, a collaborative research team led by Dr. Yousuke Furuta in Toyama Chemical Co., Ltd and Dr. Kimiyasu Shiraki in University of Toyama screened their compound libraries and discovered a novel small molecule with anti-influenza activity, called favipiravir (T-705) (Fig. 1). They found that favipiravir shows a potent antiviral activity against all influenza A, B, and C viruses without cytotoxicity *in vitro*. Strikingly, they also demonstrated that oral administration of favipiravir (200 mg/kg/day) for 5 days completely protects mice from lethal H1N1 influenza A virus infection. It was later shown that favipiravir-RTP, an active form of favipiravir, inhibits influenza RNA-dependent RNA polymerase activity without affecting cellular RNA and DNA polymerase activity. Although the exact mechanism of action remains unclear, it is being hypothesized that favipiravir-RTP may be incorporated into the new viral RNA copies or interact with specific domains of the influenza polymerase and therefore block its function.

It is noteworthy that favipiravir is also able to inhibit replication of influenza viruses that are resistant to neuraminidase or M2 ion channel inhibitors due to their different mechanism of action, while emergence of its own resistant virus seems to be unlikely. Indeed, favipiravir effectively protects mice from infection with lethal H5N1 influenza viruses, even if they are oseltamivir resistant. In addition, favipiravir shows synergistic inhibitory effect against influenza virus infection in combination with oseltamivir, expanding options for anti-influenza therapy. These reports clearly demonstrate favipiravir is a novel and promising drug in the fight against lethal influenza infection. Unfortunately, however, favipiravir has been reported to have a risk for teratogenicity and embryotoxicity. In Japan, favipiravir was approved in 2014 for emergency preparedness stockpile for pandemic or re-emerging influenza viruses resistant to known anti-influenza drugs. In addition, a phase III clinical study for favipiravir has already been completed in USA.

There is no doubt that not only influenza virus, but also many other viruses are capable of causing human diseases and threatening public health. Favipiravir has been shown to exhibit antiviral activity against a wide range of RNA viruses including Ebola, Zika, West Nile, and rabies virus, suggesting that this compound could have a potential to counteract re-emerging and/or novel pathogen for which no antiviral therapy is available.

3 Ivermectin (STROMECTOL®)

Yu Ichida and Yumiko Imai

Laboratory of the Regulation for Intractable Infectious Diseases, National Institute of Biomedical Innovation, Health and Nutrition

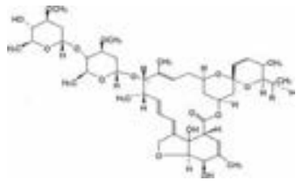

Fig. 2. Structure of Ivermectin (Crump and Ōmura S. Proc Jpn Acad Ser B Phys Biol Sci. 2011; 87:13-28).

Ivermectin (IVM, Fig. 2) is one of the best known and widely used anti-parasitics in human and animal medicine. To date, IVM has impacted human health. Millions of people in the poorest countries had suffered from onchocerciasis (river blindness), strongyloides (threadworm), and lymphatic filariasis (elephantiasis) before the discovery of antiparasitics by Satoshi Ōmura at Kitasato University and William Campbell at Merck company. They discovered avermectin in Japanese soil and developed IVM, which is derivatives of avermectin. IVM is safe and strongly combats parasitic disease, thus contributing to global human health. Their discovery was the joint focus of the 2015 Nobel Prize in Physiology or Medicine, showing the importance of avermectin and Japan's contribution to supporting global human health.

In general, it is very difficult for discovering target microbes in soil. However, Dr. Ōmura worked on discovering target microbes hard and he discovered them after *great effort* and struggle. In 1974, Dr. Ōmura at Kitasato University collected a sample of soil from a golf course in Itou city, Shizuoka, Japan. Dr. Ōmura isolated and cultured a Gram-positive bacterium (NRRL 8165, unknown species of *Streptomyces*), and this was sent to Dr. Campbell at Merck to test for anti-parasitic effects. NRRL 8165 cultures showed potent activity against *Heligomosoides polygyrus* infection in mice, and active components were purified, revealing macrocyclic lactones family. Dr. Ōmura named these naturally occurring compounds avermectins. Avermectins are a mixture of four compounds, avermectin A_1, A_2, B_1, and B_2. IVM is modified chemically using avermectin B_1 and showed potent activity against a broad array of parasitic nematodes via oral and parenteral administration. IVM has activity against various arthropods and is safe for most mammals.

IVM affects nematode motility, feeding, and reproduction. IVM binds to glutamate-gated chloride channels (GluCls), which are expressed in invertebrate nerve and muscle cells, resulting in an increase in the permeability of the cell membrane to chloride ions. This induces hyperpolarization in the nerve or muscle cell, causing paralysis and death of the parasite. While GluCls are expressed in nematode motor neuron commissures, lateral or sublateral nerve cords, and pharyngeal neurons, GluCls are not present in vertebrates. IVM interacts with other ligand-gated chloride channels activated by gamma aminobutyric acid (*GABA*). For this reason, IVM has nematode-specific effect. IVM also interferes with nematode fertility by inhibiting the production of microfilariae. The affinity of IVM against mammalian cells is very low and IVM can't pass readily blood-brain barrier. Thus, IVM has broad safety and exerts high attack ability against various nematodes.

4 Fasudil (Eril®)

Toshio Asano

Asahi Kasei Co., Ltd.

A Rho kinase inhibitor fasudil (FAS) (Fig. 3) is honored to be the first approved kinase inhibitor in the world. Its discovery research began from encounters with a neurosurgeon. I heard that there were many cases of death due to the subsequent occurrence of cerebral vasospasm even if the patient underwent surgery for subarachnoid hemorrhage (SAH) successfully. Many reports indicated that cerebral vasospasm after SAH was mainly caused by extreme narrowing of cerebral blood vessels. The mechanism of the narrowing had been unknown. Despite many attempts, there was no effective therapeutic drug for the cerebral vasospasm yet.

Although various substances were proposed and considered to be the cause of cerebral vasospasm, no anti-substance therapy was effective. Therefore, we focused on phosphorylation of myosin light chain (MLC), which is a common pathway of vasoconstriction. We hypothesized that reducing MLC phosphorylation in blood vessels would be effective for preventing cerebral vasospasm. Asahi Kasei had synthesized various kinase inhibitors to research intracellular signal transduc-

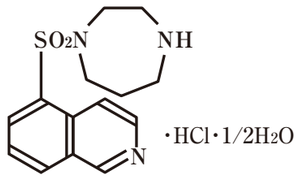

Fig. 3. Structure of fasudil.

tion, so we thought that we could make use of our knowledge. In order to make Asahi Kasei's pharmaceutical business successful, we were aiming to develop new drugs to treat diseases with significant unmet medical needs. We defined a target product profile and began the process of drug discovery. We screened many compounds using various assay systems such as kinase inhibition, vasorelaxation, reducing MLC phosphorylation and so on. Finally, we discovered FAS showing unique pharmacological action based on Rho kinase inhibition. Meanwhile, we understood that many neurosurgeons consider a drug candidate's effectiveness for canine two-hemorrhage model (SAH model) to be a key point. This is because there had been no report on drugs that showed effect for the model by systemic administration until then. As we published a paper showing that FAS was effective on this model, we gained a great deal of attention. The clinical penetration of FAS after approval is extremely high. There is an investigational report that 77% of patients suffering SAH are administered FAS.

The main difficulties of FAS's research and development were as follows. Since the pathophysiology of cerebral vasospasm was unknown, we had to conduct a variety of basic research for the first time. The functions of kinases were unknown in the pathogenesis of many vascular diseases. Also, since FAS was obviously a first-in-class drug, we had to carefully examine adverse effects caused by FAS.

Following FAS, kinase studies became extremely active and several kinase inhibitors have been developed. The discovery of FAS was the pioneering accomplishment which opened the path to a large number of kinase studies, and is recognized as having greatly influenced the world's drug research and development.

5 Candesartan cilexetil (BLOPRESS®)

Masakuni Noda[1] and Kohei Nishikawa[2]

[1]Regenerative Medicine Unit and [2]Former senior researcher, Pharmaceutical Research Division, Takeda Pharmaceutical Company

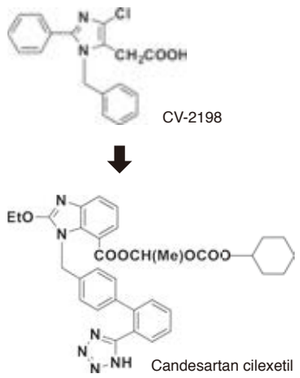

Fig. 4.
Structures of CV-2198 and Candesartan cilexetil

Candesartan cilexetil (TCV-116), an AT_1 receptor antagonist, is originally developed in Takeda Pharmaceutical Company and it becomes one of the representative angiotensin II (AngII) receptor blockers (ARBs). It is known to show potent and long-lasting pharmacological effects and it is approved for patients with hypertension as well as chronic heart failure.

A lead compound of candesartan cilexetil, CV-2198, was synthesized in the research of a novel synthetic chemical reaction using ADAN (2-amino-3,3-dichloroacrylonitrile) as a starting material in Chemistry Research Laboratories of Takeda. It was also the compound tested 2198th in an *in vivo* random screening using rats to find out new diuretic compounds, which was coincidentally conducted in Biology Research Laboratories in Takeda. CV-2198 showed a potent diuretic effect, but no other pharmacological effect in a variety of screening systems. The combination of the basic research on the novel synthetic chemical reaction and the discovery of its only diuretic action seemed to be a surely happy encounter described as probably "Serendipity".

In the mechanistic studies of the diuretic effect of CV-2198, interestingly it had antihypertensive effects at the low dose which did not show the diuretic effect. Eventually, the team found that CV-2198 specifically inhibited AngII-induced contraction of blood vessels. It was the moment that non-peptide ARB, having the imidazole acetic acid moiety as a core chemical structure, was discovered for the first time in the world. This finding made it possible to identify losartan, candesartan cilexetil and other ARBs.

Although the most potent compound among CV-2198-related compound, CV-2973, was forwarded to clinical trials, unfortunately, its efficacy was not observed. The drug discovery of ARBs in Takeda was once terminated in 1982 after submission of CV-2198-related patents. In 1989, Du Pont's research group surprisingly reported an ARB, losartan, which was synthesized based on the Takeda's patents, describing the inhibitory effects of about 200 imidazole acetic acid derivatives including CV-2198 and CV-2973 on the AngII-induced vasoconstriction. Takeda resumed the research of ARB and employed the robust *in vitro* and *in vivo* assay systems, which were established by pharmacologists in previous ARB research. The systems contributed to the discovery of candesartan cilexetil, exhibiting the superior profiles to losartan, within the short period of time.

Candesartan cilexetil is a prodrug and its active metabolite is candesartan (CV-11974), an AT_1-selective-competitive antagonist. CV-11974 reduced the AngII-induced maximal vasoconstriction and its antihypertensive effect was potent and long-lasting in rats. The mechanism of those profiles was suggested to be attributable to its slow dissociation of CV-11974 from AT_1 receptors. This property is considered to be related to the potent and long-lasting antihypertensive effect at low doses in the clinical setting.

6 Donepezil hydrochloride (Aricept®)

Hachiro Sugimoto[1,2], Yoshiharu Yamanishi[1], Yutaka Tsuchiya[1], Hiroo Ogura[1], Yoichi Iimura[1], Kiyomi Yamatsu[1]

[1]Eisai Co., Ltd., [2]Doshisha University Graduate School of Life and Medical Sciences

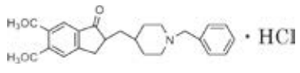

Fig. 5.

Fig. 6.
Donepezil hydrochloride (Aricept®)

Donepezil hydrochloride (Fig. 6) activates the cerebral cholinergic nervous system by increasing the cerebral acetylcholine (ACh) level through reversible inhibition of an acetylcholine (ACh)-degrading enzyme, acetylcholine esterase (AChE). Donepezil hydrochloride is indicated for the treatment of dementia of the Alzheimer type.

When development of a therapeutic agent for Alzheimer's disease was planned in 1983, we focused on the structure of tacrine. Tacrine was a known acetylcholine esterase (AChE) inhibitor, but it also had high toxicity. Thus, we tried to synthesize a tacrine derivative that did not cause liver dysfunction, but it was still not possible to avoid toxicity. Compound (1) was incidentally discovered as an AChE inhibitor in an unrelated study. Using (1) as a lead compound, we were successful in synthesizing Compound (2), which we found to be the strongest known AChE inhibitor. However, we then found that 98% of Compound (2) is degraded in the liver in dogs. The study was terminated at this point, but we still believed that we could be successful by improving the pharmacokinetics of Compound (2), and we re-established the project under a different name. The study period was only extended by one year, but we single-mindedly synthesized and evaluated compounds day after day, and finally succeeded in synthesis of a molecule, donepezil hydrochloride (product name: Aricept), that had satisfactory pharmacokinetics.

A rat learning disability model in which the basal forebrain (NBM) is destroyed can be produced using a neurotoxin, ibotenic acid. In this model, the cerebral ACh content decreases and shows learning disability. When a normal rat is placed in a bright room, the rat enters an adjoining dark room due to nocturnal animal behavior, and when electricity flows on the floor to shock the rat entering the dark room, the normal rat learns that entering this room is dangerous. In contrast, a rat with a destroyed NBM enters the dark room again when it is placed in the bright room because of its learning disability. The efficacy of Aricept was judged based on extension of the time to entering the dark room by the drug. Oral administration of Aricept exhibited a significant effect in extending this time.

Discovery of a lead compound was difficult, and Compound (1) was eventually discovered by accident and as a surprise. We also had difficulty improving the bioavailability, even though we developed Compound (2) as the strongest known inhibitor of AChE. Moreover, the results of a phase 2 study in Japan did not show dose-dependence, but the outcomes of a subsequent clinical study in the US were excellent. Thus, the work performed in the US allowed the study to move ahead and to be successful.

7 Naldemedine (Symproic®)

Toshiyuki Kanemasa, Ph.D.

Drug Discovery & Disease Research Laboratory SHIONOGI & CO., LTD.

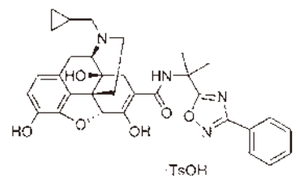

Fig. 7.
Structure of naldemedine.

Opioid analgesics such as morphine are mainly used for palliative care in Japan and are widely used for moderate or severe non-cancer pain in the US. While opioid analgesics exhibit excellent analgesic effects, they also have adverse effects. The incidences of nausea/vomiting, constipation, and sleepiness are particularly high, and opioid analgesics interfere with pain control, which may result in their discontinuation. A non-clinical study found that morphine induces nausea/vomiting and constipation at a low dose, rather than at the analgesic dose.

Based on a proposal by Professor Suzuki of Hoshi University (discovery of a δ opioid receptor-selective antagonist as a treatment for opioid-induced nausea/vomiting), we started a drug discovery project with the aim of better pain control to contribute to improvement of QOL of patients suffering from opioid-induced adverse effects. In this project, we searched for a periphery-selective antagonist that would block adverse effects (constipation and nausea/vomiting) without influencing the central action (analgesic action), with the aim of development of a peripheral opioid receptor antagonist.

Naltrexone inhibits adverse effects of opioids, but simultaneously influences analgesic action. Thus, we initiated a search for a compound with high oral absorption, but low blood-brain barrier permeability. It was very difficult to find a compound with these concomitant characteristics, but we acquired naldemedine (Fig. 7), which has the target profile, by introducing a carbamoyl group at position 7 of the morphinan skeleton. Naldemedine showed potent antagonism against μ, δ, and κ opioid receptors (0.5, 0.27, and 3.13 nM, respectively), and inhibited morphine-induced suppression of

dye transport in the small intestine in rats in a dose-dependent manner (oral ED_{50} of 0.03 mg/kg). In contrast, in a rat tail flick test, inhibition of morphine-induced analgesic action occurred only at a very high dose (≥10 mg/kg), showing a large difference from the anti-constipation effect in the small intestine transport capacity test. In addition, administration of naldemedine at the pharmacological dose did not induce central withdrawal symptoms in morphine-dependent rats, with a 30 times difference from the anti-constipation effect. This may be due to low transfer of naldemedine into the brain.

The combination of a potent anti-constipation effect without influencing the analgesic action of the opioid found in the non-clinical study was also observed in a clinical study, in which 0.2 mg of naldemedine improved opioid-induced constipation regardless of the dose of opioid analgesics and had no effect on the analgesic action of the opioid.

8 Erythropoietin

Erythropoietin is now administered to most patients with renal anemia, and its market value has reached several trillion yen worldwide. Dr. Takaji Miyake succeeded in preparation of purified human erythropoietin from 20 tons of urine in 1976, after starting this work 13 years earlier in 1964. Extraction at low temperature was necessary, but no low-temperature room was initially available and all windows were opened for column operation in midwinter. Subsequently, a low-temperature room to facilitate purification was made from an assistant's room at the university, and nearly 3,000 rats were used each year to measure its activity. The work was published in 1977, the human erythropoietin gene was cloned using the purified preparation in 1985, and a clinical trial of recombinant erythropoietin was initiated in the same year, opening the way to treatment of renal anemia today. Discovery of erythropoietin is an excellent example of creation of a new drug by the tenacious research efforts of Japanese scientists.

9 Carperitide(Atrial natriuretic peptide (ANP))

Dr. Kenji Kangawa, National Cerebral and Cardiovascular Center Research Institute, discovered the atrial natriuretic peptide (ANP) in the atrium, and published this finding in 1984. Subsequently, ANP was developed as a drug for treatment of acute heart failure or as a diagnostic agent for heart failure in Japan. This process provides an excellent example of the success of translational research all over the world. It should be mentioned that isolation of ANP from the human atrium and determination of the structure of ANP were completed within two months after study initiation, using the original peptide analysis technique of Dr. Kangawa. The pathophysiological functions of ANP, such as its blood pressure-lowering and diuretic actions, were determined soon afterwards. This is a good example of establishment of proof of concept and acceleration of drug discovery by Japanese science and technology. Synthesis of brain natriuretic peptide (BNP) in the brain was also discovered by Dr. Kangawa, and this finding was published in 1988. BNP is synthesized and secreted in the ventricle in the periphery, and is now the most commonly used diagnostic agent for heart failure. It is also used as a drug for treatment of heart failure in the US and other countries. Thus, ANP and BNP are now used as diagnostic agents and drugs for heart failure worldwide.

10 Febuxostat (Feburic®)

Febuxostat is a uric acid synthesis inhibitor with no purine skeleton that was developed by Shiro Kondo and co-workers at Teijin Ltd. Inhibitors of uric acid synthesis include allopurinol, a derivative of a uric acid precursor, hypoxanthine. Allopurinol was launched in the 1960s as an inhibitor of xanthine oxidase (XO), a uric acid-synthesizing enzyme, and is still in use. Many inhibitors of XO have been synthesized thereafter, but no drug superior to allopurinol has been developed and allopurinol has monopolized this market. In this context, febuxostat has emerged as a novel non-purine selective inhibitor of XO.

The mechanism underlying the clinical efficacy of allopurinol is more complicated than first thought. The XO inhibitory activity of allopurinol is actually relatively weak, but its major metabolite, oxypurinol, is a potent XO inhibitor. Kondo believed that the major cause of unsuccessful development of new XO inhibitors was insufficient inhibitory activity, and first he searched for compounds having a potent inhibitory effect on XO. Since adverse effects due to the purine skeleton were of concern, he focused on compounds with no purine skeleton. The basic structure was changed from a purine skeleton to one comprised of single-bonded five- and six-membered rings, and several mother nuclei were synthesized. Of these, phenylthiazole carboxylic acid showed weak inhibitory activity on XO, and several potent XO inhibitors were acquired relatively smoothly using this molecule as a lead compound.

From this point, there were several further difficulties. The acquired compounds were administered to mice, but the expected effect of a uric acid decrease was not observed. Synthesis and evaluation in mice were repeated for one year, and finally this effort was rewarded when the basic structure of a compound showing strong activity in mice was identified. More than 10 candidate compounds were then prepared. However, another major obstacle blocked the way, since mutagenicity was detected for all of these compounds. Discontinuation of development crossed Kondo's mind, but a compound without mutagenicity was acquired by reinvestigation of the stereochemistry around the nitro group, which was considered to be the cause of mutagenicity. In addition, a compound in which the nitro group was converted to a cyano group also exhibited an equivalent or higher uric acid-decreasing effect. Finally, febuxostat, which has the cyano group, was tested in a clinical trial.

The first clinical trial of febuxostat was initiated in 1995, and the drug was launched in 2009 in the US and 2010 in Europe, ahead of Japan, where it was launched in 2011. One reason for prolongation of the clinical trial was that the uric acid-decreasing effect of febuxostat was observed at a dose lower than expected based on the phase I study, and dose-setting was redone. Fewer side effects were also found and dose reduction was not necessary for patients with renal failure because, unlike allopurinol, febuxostat is excreted in feces, as well as in urine. Thus, 23 years after its conception, an inhibitor of uric acid synthesis with many advantages over allopurinol was introduced for the first time in about 40 years.

11 Nalfurafine (Remitch®)

Hiroshi Nagase

Specially Appointed Professor (April 1, 2018)

World Premier International Research Center Initiative (WPI)
International Institute for Integrative Sleep Medicine (IIIS)
Nagase Laboratory (Medicinal Chemistry)

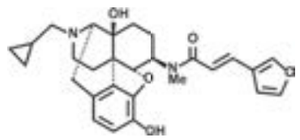

Fig. 8.
nalfurafine

Since opioid receptors have been classified into three types, μ, δ, and κ, and drug dependence has been reported to be derived from the μ receptor, a fierce competitive race for the development of κ agonists began. In this regard, we successfully developed a novel compound with an N terminal partial structure of endogenous opioid peptides[1,2]. As most of the U-50488H-type κ-agonists without the partial structure of endogenous peptides cause severe drug aversion (hallucination, auditory hallucination), these compounds were rejected after the initial phase of clinical trials. Only our κ agonist, nalfurafine, successfully developed by Toray Industries inc., caused neither drug dependence nor aversion. However, because of its severe sedative effect causing excess sleepiness, nalfurafine was not applied to the postoperative pain. At this stage, the development of nalfurafine as an analgesic was resigned. We inevitably searched for other indications of nalfurafine. At the same time, the antipruritic effect of the κ-agonist in an animal model for itch were reported—a period when there were no specific drugs to treat intolerable itch in kidney dialysis patients. We therefore decided to develop nalfurafine as an antipruritic drug. On the basis of the excellent results of the clinical trial, Toray obtained the manufacturing license for nalfurafine in 2009 and Torii Pharmaceutical released the drug (trade name: Remitch® capsule). The post-marketing surveillance studies reported more than 80% efficacy in terms of its antipruritic effect. Remitch® has also been applied to treat severe itch in patients with hepatic failure and its sales have been growing steadily. The advantage of Remitch® is its few serious side effects owing to the minute dose required (2 μg/kg body weight). Furthermore, as itch was not recognized as a disease, patients had to tolerate it due to a lack of specific drugs. Following the release of Remitch®, itch has been recognized as an actual disorder and is being actively treated. Moreover, studies on the basic mechanisms of itch have also been gradually increasing. Eventually, by collaborating with Dr. Ross's group at the University of Pittsburgh, we clarified

the reason why people have a tendency scratch when they feel an itch, which had been a mystery for a long time[3].

Ideas leading to the development of the drug:
I obtained the ideas when I was studying at the University of Minnesota—that is, the message–address concept as well as the partial structure and accessory site of endogenous opioids.

Pharmacological effects of the drug:
Nalfurafine does not bind to receptors other than the opioid receptors because of the presence of a specific morphinan skeleton. Nalfurafine does not cause drug dependence. Additionally, nalfurafine does not cause drug aversion, unlike the U-50488H type κ agonists developed by other drug companies.

Difficulties faced during development:
We had to abandon the development of nalfurafine as an analgesic because of its sedative effect.

12 Selexipag

Nippon Shinyaku started development of prostacyclin (PGI_2) receptor agonists almost 20 years ago. PGI_2 is an endogenous substance that induces vasodilatation via an activation of PGI_2 receptor (IP receptor). Based on its efficacy, PGI_2 was used as medications, but the extremely short half-life of PGI_2 had been a drawback. Therefore, PGI_2 analogues with improved half-lives were synthesized, but new drugs with a more long-acting profile were still desired.

So, we have continued to explore an orally available and long-acting IP receptor agonist, and finally discovered selexipag (development code, NS-304; product name, Uptravi® in tablet form) with a nonprostanoid structure. Selexipag is metabolized into MRE-269 after oral administration, and the long duration of effective plasma concentration of MRE-269 is maintained. MRE-269 acts as a potent and highly selective IP receptor agonist.

Although we first considered arteriosclerotic disease to be an indication for selexipag, we determined that pulmonary arterial hypertension (PAH) was more appropriate as a potential indication in terms of its pharmacological profile. PAH is a rare, life-threatening disease characterized by an abnormal increase in pulmonary arterial pressure. There had been no adequate cure for PAH over the past decades. Since then, the continuous intravenous infusion of PGI_2 has been introduced as a treatment for PAH, and the prognosis of PAH has been markedly improved. However, this therapy impairs patients' quality of life (QOL). Therefore, many kinds of orally available drugs have been produced for PAH, but the continuous intravenous PGI_2 therapy has remained the most effective. Thus, we have selected PAH as the indication for selexipag because an oral long-acting IP receptor agonist would be useful for PAH.

We first conducted the drug development in Europe because it was difficult to perform clinical trials in Japan due to the number of patients. In the Phase I clinical trial, the half-life of MRE-269 was about 8hr after the administration of selexipag, indicating good pharmacokinetic properties. We also confirmed the safety in the up-titration study based on the dosing regimen of selexipag.

The subsequent Phase II clinical trial was carried out in Europe. We selected pulmonary vascular resistance (PVR) as a primary endpoint. As a result, the primary endpoint was met in spite of difficult situation that all patients received existing therapies for PAH. This success of the Phase II clinical trial was the critical point of the further development plan. After that, the global, double-blind, placebo-controlled, Phase III trial (GRIPHON trial) enrolling 1,156 patients from 39 countries was conducted. The primary endpoint, the time to clinical worsening, was met with statistical significance (reduced by 40% with selexipag compared to placebo). The efficacy of selexipag was also demonstrated in the open-label, Phase II clinical trial in Japan with the primary endpoint of PVR.

As mentioned above, selexipag, with a long-acting profile and high selectivity to IP receptor, has demonstrated the efficacy for PAH through clinical trials. Selexipag was approved in September 2016 and launched in November 2016 in Japan. The clinical trials in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and arteriosclerosis obliterans (ASO) are being conducted in Japan. The indications for selexipag will be expanded in the future.