

Aiming at Developing Original New Drugs to Global Standards



Ono's research and development principle is to "Deliver our contributions to society by developing drugs that truly benefit patients". We put this into practice by tackling diseases that remain unconquered as yet and areas that are high in healthcare needs where patient satisfaction of treatment is still low.

This principle delineates the management policy of our R&D activities, which are:

1. Focus on areas where the technologies and know-how accumulated over our long history can be optimized
2. Tackle new areas (i.e. membrane transport controllers, biotechnology based medicines)
3. Utilize breakthrough drug discovery seeds and leading-edge technologies from the world over
4. Pursue quality and speed of research

Aiming at develop new drugs to global standards, our tireless effort continues.

With Outstanding Technology and Know-how, Producing Original New Drugs to Global Standards

To develop original new drugs to global standards, Ono is engaged in drug discovery research based on accumulated technologies and know-how – in areas where our strengths can be fully exploited (i.e. bioactive lipid agonists and enzyme inhibitors such as proteases and kinases), as well as in areas offering new challenges. The latter includes modulators of membrane transport system such as ion-channels and transporters as well as biotechnology based medicines. This is an area where our know-how from neuroscience research and our gene assets can be effectively deployed. Using the latest information acquired from global research institutions on drug discovery targets and the cutting-edge drug discovery technologies that biopharmaceutical companies have to offer, we will drive forward our R&D.

Drug Discovery to Fulfill the Unmet Medical Needs of Frontline Healthcare

The probability of a new substance discovered during basic research turning into an approved drug is 1 in 20,000. The discovered compound takes ten years or more to reach patients as a new drug. The cost of developing a new drug amounts to 50 billion yen or even 100 billion yen. Thus, the development of a new drug is the fruit of many years of labor and massive R&D expenditures.

However, no matter how much time and money are spent, the successful

development of a new drug is not a certainly by any means.

The reality is a worldwide decline in the success rate of development of new candidate compounds with innovative mechanisms. In this context, Ono is dedicating effort into the discovery of drugs that fulfill the unmet medical needs at the frontline of healthcare.

A Research Structure that Breeds Motivation and Fresh Ideas

The development of original new drugs is driven by the motivation of individual scientists and their ability to think along new paths. Ono sets out clear research targets to enhance such motivation and creative thinking of its researchers. Our research organization is based on project teams whose members have cutting-edge expertise in different areas.

Refining the Most Advanced Techniques and Data to Develop New Drugs

Research to develop new drugs is the lifeline of any pharmaceutical manufacturer. Ono has a distinguished record of creating many first-in-class drugs, and our ongoing basic and applied research programs serve the goal of continued development of original new drugs.

(Tsukuba)

Tsukuba Research Institute consists of Exploratory Research Laboratories and Pharmacokinetic Research Laboratories. The former utilizes the latest genome techniques to identify compounds with

therapeutic potential and investigates the links between various compounds and diseases, and the latter conducts pharmacokinetic research for new compounds discovered by Ono.



Tsukuba Research Institute in Ibaraki

(Minase)

Medicinal Chemistry Research Laboratories is engaged in the discovery of new drug candidate compounds. Exploiting the know-how gained from research into prostaglandin, state-of-the-art synthesis technology and information on three-dimensional (3D) structure of proteins, the Laboratory utilizes computer aided theoretical drug designing technology to produce new compounds with potent pharmacological and physico-chemical properties as well as better safety profiles. Discovery Research Laboratories and Development Research Laboratories employ original screening methods and



Minase Research Institute in Osaka

disease models to identify compounds that act on unique targets, evaluating them for their effectiveness as pharmaceutical products, and strives to discover and develop new drugs that are highly innovative and original.

Pharmaceutical Development Laboratory conducts research into drug formulation of candidate drugs as well as their quality assurance as pharmaceutical products.

(Fukui)

Studies using state-of-the-art equipment at the Fukui Safety Research Laboratory cover the potential general toxicity, carcinogenicity, reproductive toxicity, and genotoxicity of compounds under evaluation for pharmaceutical use.

The Fukui Chemical Process Research Laboratory conducts research to enable large-scale synthesis of drug substances for mass production, actively developing synthesizing techniques required for mass production and reducing costs.



Fukui Research Institute in Fukui

Searching for Original and Innovative New Drugs, in Japan, Europe and the US

Patients suffering from disease are found in all corners of the globe. It is Ono's earnest desire to deliver to patients worldwide original and innovative new drugs that fulfill

the needs found at the frontline of healthcare. This has led to the marketing of many prostaglandins and enzyme inhibitors. In clinical development, we aim to achieve speedy confirmation of the efficacy and safety of original and innovative new drug candidate compounds. In our three bases in Japan, Europe and the US, we conduct development on drugs to treat many diseases. Our hope is to deliver a new drug as quickly as possible into the hands of patients who are suffering from the ravages of a disease that has yet to be conquered. We endeavor to increase the likelihood of success by conducting clinical trials based on our knowledge of the properties of the compounds. Based on the mechanism of action of compounds under development, we conduct trials on patients for whom greater efficacy seems more promising. Outside Japan, work is not restricted to development projects pursued by Ono alone. We promote clinical trials that are being conducted by our affiliated biopharmaceutical companies.

Global Clinical Development

Faced with the challenge of emerging victorious in the ever intensifying global competition in drug development, Ono is placing topmost priority on gaining approval in Europe and the US. Thus Ono's policy is for clinical development to be led by European and US efforts.

In May 2008, Global Development Headquarters was established within Ono Pharma USA (OPUS), epitomizing the effort to strengthen our international clinical development centering on the United States. Global Development Headquarters coordinates with both the clinical development units in OPUS and in the UK subsidiary, Ono Pharma UK (OPUK),

making steady achievements in clinical development in Europe and the US. With the clinical development fully set up overseas, Ono is now taking part in multinational clinical trials, enabling us to actively conduct development in Japan taking advantage of the results from the multinational clinical trials and other international studies conducted ahead of Japan, thereby ensuring faster development speed.

Strategic Partnerships with Bio-pharmaceutical companies As Well As Academic and Research Institutions Worldwide

Global Discovery Research Alliance Headquarters set up in May 2008 in Ono Pharma USA, Inc (OPUS), our US subsidiary, actively promotes drug discovery collaboration with the US and European bio-pharmaceutical companies and research collaboration with academic institutions and research institutions. The resulting exploration of breakthrough drug discovery seeds and importing of leading-edge technologies will serve to strengthen Ono's drug discovery activities.

In discovery alliance with bio-pharmaceutical companies, we aim to form partnerships in areas where we can exploit the technologies

and know-how we accumulated through our priority research hitherto and where we can show our strengths in future (namely, kinase, ion-channel, bioactive lipids, biotechnology based medicines).

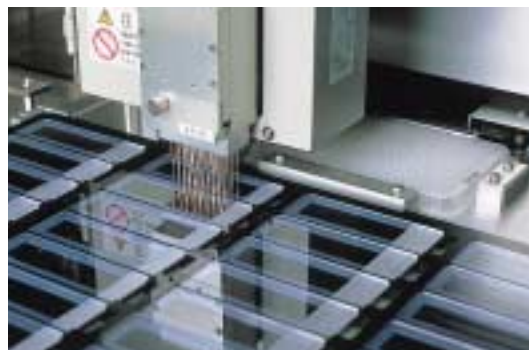
In the kinase area, our drug discovery alliances are with the US companies, Array BioPharma Inc. and Locus Pharmaceuticals, Inc., and drug discovery efforts are underway based on kinase inhibitors, which are associated with various diseases.

The initial contract research period with Array BioPharma has expired. The success story here is in the discovery of several compounds with powerful kinase inhibiting properties, thanks to Array's expertise in protein X-ray crystallography.

In conjunction with Evotec AG of Germany, drug discovery effort is ongoing in the area of small molecule compounds that inhibit protease action which is associated with many diseases, offering the promise of fulfilling unmet medical needs. In ion-channel and bio-active lipids, alliance talks are underway with bio-pharmaceutical companies and universities.



3-D Molecular Modeling



Preparation of DNA Microarrays

Improving Development Pipeline through Strong In-Licensing Effort of New Drug Candidate Compounds

To reinforce the development pipeline, Ono is making strong efforts to in-license new drug candidate compounds from drug companies and bio-pharmaceutical companies in the US and Europe.

In 2006, Ono in-licensed a new drug candidate for cancer anorexia/cachexia from Sapphire Therapeutics, Inc. of the USA (now Helsinn Therapeutics (U.S.), Inc.).

In 2007, a short-acting general anesthetic from CeNes Ltd of the UK (now PAION AG, Germany) was in-licensed and a therapeutic agent for thrombocytopenia was also in-licensed from Nissan Chemical Industries, Ltd.

In October 2008, Ono acquired from Progenics Pharmaceuticals, Inc. of the USA

an exclusive right to develop and commercialize methylnaltrexone bromide in Japan, a drug for the treatment of intractable constipation induced by narcotic analgesic.

All these successes in licensing partnerships contribute to the steady strengthening of Ono's development pipeline.

Because European and American bio-pharmaceutical companies are the target for our licensing activities, Global Business Development & Licensing was established within OPUS on July 1, 2009. The fulcrum of activity has thus been shifted from Japan to the US. With Global Business Development & Licensing at the helm, coordinated effort will continue together with the business development units in Japan and in OPUK to actively in-license new candidate compounds not only in early development stages (pre-clinical or Phase I) but in late development stages as well.



New Drugs in Development (as of August 2009)

In our ongoing effort to create products that will promote the health of more people worldwide, Ono has many new drug formulations under development, including the following major drugs:

Emend® Capsules (ONO-7436 / MK-0869)
Emend® is the first neurokinin (NK) 1 receptor antagonist in the world. The drug is effective not only for acute phase of chemotherapy-induced nausea and vomiting, but also for delayed phase (24 hours or later after start of chemotherapy) for which there was no effective drug.

Japan: NDA filed / Chemotherapy-induced nausea and vomiting
Phase III / Chemotherapy-induced nausea and vomiting in children
Overseas: Marketed (Merck & Co., Inc.)

Glactiv® Tablets (ONO-5435 / MK-0431)
Glactiv®, a dipeptidyl-peptidase (DPP) IV inhibitor, is a new class of drug for type II diabetes and is expected to be useful for control of postprandial hyperglycemia with low risks of hypoglycemia and weight gain in type II diabetes patients.

Japan: NDA filed / Type II diabetes (co-development with Banyu Pharmaceutical Co., Ltd.)
Phase III / Type II diabetes (combination therapy with α -glucosidase inhibitor; co-development with Banyu Pharmaceutical Co., Ltd.)
Phase III / Type II diabetes (combination therapy with insulin; co-development with Banyu Pharmaceutical Co., Ltd.)
Overseas: Marketed (Merck & Co., Inc.)

Rivastach (ONO-2540 / ENA713D)
(transdermal patch)

Rivastach or rivastigmine patch is a drug for the treatment of Alzheimer's disease with an inhibitory action on both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). The drug inhibits not only AChE which is known as an enzyme deeply involved in Alzheimer's disease, but also BuChE which reportedly increases as the disease progresses.

Therefore, the drug is expected to have an effect in patients who do not respond to existing drugs. *Rivastach* is the first transdermal treatment developed for the disease and is expected to provide greater convenience, e.g. caregivers can easily confirm the administration of the drug.

Japan: Phase III / Alzheimer's disease (co-development with Novartis Pharma K.K.)
Overseas: Marketed (Novartis AG)

ONO-7847 / MK-0517 (injection)

ONO-7847 is a neurokinin (NK) 1 receptor antagonist being developed for the prevention of chemotherapy-induced nausea and vomiting. It is the prodrug of ONO-7436 / MK-0869 (*Emend® Capsule*) which makes it available in injectable form.

Japan: Phase III / Chemotherapy-induced nausea and vomiting
Overseas: Phase III / Chemotherapy-induced nausea and vomiting (Merck & Co. Inc.)

ONO-7643 / RC-1291 (tablet)

ONO-7643 is a small-molecule ghrelin mimetic being developed for cancer anorexia / cachexia. The drug has similar pharmacological actions to ghrelin, a circulating peptide hormone with multiple physiological actions, including appetite stimulation, muscle-building (anabolic) and modulation of gastrointestinal functions. The compound is therefore expected to be a breakthrough drug that improves quality of life (QOL) for patients impaired by a systemic wasting condition characterized by anorexia, lipolysis and muscle loss associated with the progression of cancer.

Japan: Phase I / Cancer anorexia / cachexia

US & Other Countries: Phase II / Cancer anorexia / cachexia (Helsinn Therapeutics (U.S.), Inc.)

ONO-5334 (tablet)

ONO-5334, a cathepsin K inhibitor, is being developed for osteoporosis with a novel mechanism of action. Unlike bisphosphonates, the drug only inhibits bone resorption without having impact on bone formation.

Japan: Phase I / Osteoporosis

Europe: Phase II / Osteoporosis

ONO-8539 (tablet)

ONO-8539 is a selective antagonist of EP1, one of subtype receptors of prostaglandin E₂, and overactive bladder is the first indication for its clinical development program. It is expected that the drug can be given to the patients who have complications with glaucoma, for which use of anticholinergics is limited due to its mechanism of actions, and with lower urinary tract obstruction including benign prostatic hypertrophy.

Japan: Phase I / Overactive bladder

Europe: Phase II / Overactive bladder

ONO-4641 (tablet)

ONO-4641 is a sphingosine-1-phosphate (S1P) receptor agonist, being developed for the treatment of multiple sclerosis. The drug is a low molecular weight substance that keeps lymphocytes in lymph nodes and reduces the lymphocyte count in the blood, as a result inhibiting the infiltration of lymphocytes into lesions. The compound is therefore expected to be an innovative drug for the treatment of autoimmune diseases such as multiple sclerosis, which is regarded as an intractable disease.

Japan: Phase I / Multiple sclerosis

US: Phase I / Multiple sclerosis

ONO-4538 / MDX-1106 (injection)

ONO-4538, a fully human anti-PD-1 antibody, is expected to be a potential treatment for cancer and other diseases. PD-1 is one of the receptors expressed on activated lymphocytes, and is involved in the negative regulatory system to suppress the activated lymphocytes. It has been reported that tumor cells utilize this system to escape from the host immune responses. It is anticipated that blockade of the negative regulatory signal mediated by PD-1 will promote the host's immune response, in which tumor cells are recognized as foreign and eliminated.

Japan: Phase I / Cancer

US: Phase I / Cancer (co-development with Medarex, Inc.)

US: Phase I / Hepatitis C (co-development with Medarex, Inc.)

ONO-3849 (injection)

ONO-3849 is a peripherally acting mu-opioid receptor antagonist, and is developed for intractable opioid induced constipation.

Opioid pain medications are often used for the treatment of pain in cancer and other advanced illnesses, but cause constipation in many of these patients. ONO-3849 is expected to decrease the constipating effects of opioid analgesics in the gastrointestinal tract without affecting their ability to relieve pain.

Japan: Phase I / Opioid-induced constipation

Overseas: Marketed (Wyeth)

ONO-7746 (capsule) (In-licensed from Nissan Chemical Industries, LTD.)

ONO-7746 is an orally active low molecule compound which may increase platelet count by activating a receptor of thrombopoietin, which is a hematopoietic factor to accelerate platelet production. It is therefore expected to be developed as a new drug which may reduce the risk of bleeding in various diseases with thrombocytopenia and overcome risk of infection associated with platelet transfusion. Nissan Chemical is participated in co-development by process development and manufacturing of the drug substance.

US: Phase I / thrombocytopenia

ONO-5920 / YM529 (tablet)

ONO-5920 is a bisphosphonate for the treatment of osteoporosis. This is the line extension program of *Recalbon® Tablets* which was launched on April, 2009 and to offer the product in once monthly oral dosing.

Japan: Phase III / Osteoporosis (co-development with Astellas Pharma Inc.)

Onoact® for Injection

Japan: Phase III (additional indication) / Improvement of multislice CT coronary imaging ability

Elaspol® for Injection

Japan: Phase II (additional indication) / Acute respiratory failure associated with community-acquired pneumonia

