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.

Ono’s discovery research aims to identify and develop original and breakthrough pharmaceutical products truly beneficial to patients worldwide through further progress of discovery research in bioactive lipids and enzyme inhibitors, fully exploiting the technologies and know-how accumulated through prostaglandin and enzyme inhibitor research. Ono also actively takes up new challenges, entering new areas of research utilizing know-how developed through neuroscience research and gene assets obtained through genome research.

Across all these domains and areas, we are further strengthening our R&D capability by using cutting-edge drug discovery technologies acquired through alliances with biopharmaceutical companies and collaborations with academic institutions.

In clinical development, we are engaged in performing clinical studies in Japan, US and Europe, aiming to gain approval of new drugs to global standard. Faster clinical development by taking advantage of the results from multinational clinical trials and other international studies is of critical importance.

Ono aims to develop drugs that truly benefit patients. We are focusing on the areas of bioactive lipids and enzyme inhibitors as domains where the technologies and know-how that we have nurtured can be fully exploited. We are also addressing areas of new challenge so as to pioneer new domains that would enable us to make new discoveries of world-class, original, breakthrough drugs.

Bioactive lipids and enzyme inhibitors are areas of Ono’s strengths, where we can use the technologies and know-how accumulated through research into prostaglandins/leukotrienes and into enzyme inhibitors. We are engaged in drug discovery activities involving bioactive lipid signal mediators and protease/kinase inhibitors. In the areas of new challenge, we are utilizing know-how developed through neuroscience research and gene assets obtained through genome research in drug discovery efforts involving modulators of membrane transport system such as ion-channels and transporters as well as biotechnology based medicines.

Across all these domains and areas, we are propelling our R&D by using the cutting-edge drug discovery technologies that biopharmaceutical companies and academic institutions possess.
A Research Structure
Converging Knowledge and Technology

The development of original new drugs is driven by the spirit of challenge and motivation of individual scientists and their ability to think along new paths. Ono sets out high but clear targets to enhance such motivation and creative thinking of its researchers. Our research organization is based on project teams where members converge and bring cutting-edge expertise from contrasting backgrounds. The interaction within the teams stimulates and mutually enhances research achievement.

Drug discovery research is undertaken as a coordinated effort by three laboratories: the Tsukuba Research Institute, the Minase Research Institute and the Fukui Research Institute. State-of-the-art facilities for genomics and metabolomics technologies, X-ray crystallography, high-throughput synthesis and high-throughput screening are fully deployed in Ono’s efficient and speedy discovery research effort. Through drug discovery alliances with biopharmaceuticals in Europe and the USA and through research collaborations with academic and research institutions, Ono is driving forward its search for new drugs, building on the technologies and know-how accumulated in the three research institutes while effectively injecting globally leading-edge drug discovery technologies.

The Tsukuba Research Institute undertakes exploratory research for new compounds that can be “seeds” for new drugs, state-of-the-art genomics and metabolomic analysis, and pharmacokinetics of discovered compounds. The Minase Research Institute engages in medicinal chemistry research, research investigating the properties and efficacy of compounds and formulations research that can ensure quality assurance as a pharmaceutical product. The Fukui Research Institute works with safety of compounds as well as mass production and cost reduction for the clinical and commercial supply of drug substances.

Developing Original and Innovative New Drugs, - in Japan, US and Europe

Patients suffering from disease are found in all corners of the globe. It is Ono’s earnest desire to deliver to patients worldwide new drugs that fulfill the needs found at the frontline of healthcare. This has led to the introduction of many products throughout the world. Ono conducts clinical development in its three bases, Japan, US and Europe so as to achieve speedy confirmation of the efficacy and safety of original and innovative new drug candidates and to expedite new drug development that is globally viable.
Global Clinical Development

Ono is actively pursuing clinical development harnessing the three bases in Japan, US and Europe in close coordination so that it can develop new drugs on a global level. Nerve centers for clinical development have been established within the overseas subsidiaries – Ono Pharma USA, Inc. (OPUS) and Ono Pharma UK Ltd. (OPUK). Both subsidiaries are strongly pursuing overseas clinical development of Ono’s original and innovative new drug candidates. To ensure the speedy global development of new drugs, the clinical development framework is being strengthened by means such as the recruitment of more local staff.

Forging Strategic Alliances with Biopharmaceuticals and Research Institutions Worldwide

Global Discovery Alliance Headquarters established within OPUS is actively pursuing drug discovery alliances with European and American biopharmaceutical companies and research collaborations with universities and other research institutions with the aim of identifying “seeds” for new breakthrough research and geared towards injecting state-of-the-art technologies into in-house drug discovery activities.

In drug discovery alliances with biopharmaceutical companies, Ono is endeavoring to achieve its aim of discovering original and innovative new drug candidates by exploiting the state-of-the-art drug discovery technologies that these partners possess, in the domains of our strength such as bioactive lipids and enzyme inhibitors where Ono can use its accumulated technologies and know-how, and in the domains of new challenge such as modulator of membrane transport systems and biotechnology-based medicines where Ono can effectively use its accumulated know-how in neuroscience research and gene assets acquired through genome research. With respect to enzyme inhibitors, Ono is in drug discovery collaboration with Array BioPharma Inc. of the US and Ansaris, Inc. of the US, a division of Locus Pharmaceuticals, Inc for kinase inhibitors, and with Evotec AG of Germany for protease inhibitors. In the area of membrane transport systems, Ono is collaborating with Xention Limited of the UK and Evotec for drug discovery of ion-channel modulators. In March this year Ono commenced another drug discovery collaboration on bioactive lipid with BioSeek, LLC. of the US, a subsidiary of Asterand plc, utilizing BioSeek’s drug screening and analysis systems. All these collaborations are ongoing in aid of drug discovery efforts for new drug candidates in the domains of inflammation, autoimmune disease, cancer, cardiovascular diseases and CNS disorders. Ono is also eagerly pursuing alliances with universities and research institutions undertaking pioneering research work. New discovery
targets and technologies are being explored through these alliances with the aim of identifying promising compounds that may lead to breakthrough drugs.

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

Because European and American drug companies and biopharmaceutical companies are the target for our licensing activities including in-licensing of new candidate compounds, Global Business Development & Licensing was established within OPUS in July, 2009, and the fulcrum of activity has thus been shifted from Japan to the US. Global activities will become more dynamic, with efforts stepped up in in-licensing new drug candidates not only in late development stages but also in early development stages such as pre-clinical or Phase I.

While licensing opportunities of new drug candidates with innovative mechanisms are scarcer globally now, Ono has been successful in in-licensing new drug candidates: in 2006 Ono acquired the license of a novel compound for cancer anorexia/cachexia from Sapphire Therapeutics, Inc. of the USA (now Helsinn Therapeutics (U.S.), Inc.), and in 2007 a short-active general anesthetic from CeNes Ltd of the UK (now PAION AG, Germany), and a therapeutic agent for thrombocytopenia from Nissan Chemical Industries, Ltd.

Furthermore, in October 2008, Ono acquired from Progenics Pharmaceuticals, Inc. of the USA exclusive rights to develop and commercialize asimadoline in Japan, South Korea and Taiwan, which is under development in the USA for the treatment of diarrhea predominant irritable bowel syndrome (D-IBS).

**New Drugs in Development (as of August 2010)**

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:

*Rivastach® Tape* (ONO-2540 / ENA713D) (transdermal formulation)

ONO-2540 is a drug for the treatment of Alzheimer’s disease with inhibitory action on both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). It 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:** J-NDA filed / 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*) and is made available in injectable form.

**Japan:** Phase III / Chemotherapy-induced nausea and vomiting

**Overseas:** NDA filed / Chemotherapy-induced nausea and vomiting (Merck & Co. Inc.)

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,
thereby inhibiting the infiltration of
lymphocytes into lesions. The compound is
therefore expected to be an innovative drug
for the treatment of auto-immune diseases
such as multiple sclerosis, which is
regarded as an intractable disease.
Japan, US and Europe: Phase II / Multiple
sclerosis (multi-national clinical trial)

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 and muscle-building
(anabolic), and 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 is a cathepsin K inhibitor, a novel
mechanism of action, and is being developed
for osteoporosis. Unlike bisphosphonates, the
drug only inhibits bone resorption without
having any 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 the 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 those
patients who have complications with glaucoma
and with lower urinary tract obstruction
including benign prostatic hypertrophy, for
which the use of anticholinergics is limited
due to their mechanism of actions.
Japan: Phase I / Overactive bladder
Europe: Phase II / Overactive bladder

ONO-4538 / BMS-936558 (MDX-1106) (injection)
ONO-4538, a fully human anti-PD-1 antibody, is
expected to be a potential treatment for cancer
and infections 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 and viruses
are recognized as foreign and eliminated.
Japan: Phase I / Cancer
US: Phase I / Cancer and Hepatitis C
(co-development with Bristol-Myers Squibb
Company)

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 (Progenics
Pharmaceuticals, Inc.)

ONO-2745 / CNS 7056 (injection)
The drug is an innovative short-acting
general anaesthetic and sedative, and is under clinical development as a sedative agent for the induction and maintenance of general anaesthesia and for mechanical ventilation in the Intensive Care Unit (ICU). The sedative effects rapidly disappear after cessation of administration due to its metabolism by esterase enzymes, and therefore it is expected to be a drug with improved controllability and safety profile. **Japan:** Phase I / General anaesthetic  
**US:** Phase II (PAION AG)

ONO-3951 (tablet)  
ONO-3951 or asimadoline is a highly selective kappa opioid receptor agonist, and is under clinical development for diarrhea predominant irritable bowel syndrome (D-IBS).  
**Japan:** Phase I / D-IBS  
**US:** Phase III / D-IBS (Tioga Pharmaceuticals, Inc.)

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 the risk of infection associated with platelet transfusion. Nissan Chemical is participating in co-development by process development and manufacture of the drug substance.  
**US:** Phase I / thrombocytopenia

**New formulations**  
*Staybla® OD Tablets* (ONO-8025OD / KRP-197OD)  
*Staybla® OD Tablets* is the line extension program of *Staybla® Tablets*, which is a muscarinic receptor antagonist approved in Japan for the treatment of overactive bladder (OAB). The orally disintegrating (OD) tablet of the drug can be taken without water and is useful even in elderly patients, those with impaired swallowing function and those abstaining from water intake. It is expected to offer an additional treatment option on administering the drug and therefore contribute to the improvement of patient compliance.  
**Japan:** J-NDA filed / OAB (co-development with Kyorin Pharmaceutical Co., Ltd.)

ONO-5920 / YM529 (tablet)  
ONO-5920 is a bisphosphonate for the treatment of osteoporosis. This is the line extension program of *Recalbon® Tablets*. The product offers once-monthly oral dosing.  
**Japan:** Phase III / Osteoporosis (co-development with Astellas Pharma Inc.)

**Additional indications**  
*Prostandin® for Injection*  
**Japan:** J-NDA filed / Use in various vascular diagnostic testing for erectile dysfunction

*Glaactiv® Tablets* (ONO-5435 / MK-0431)  
**Japan:** J-NDA filed / Combination therapy with alpha-glucosidase inhibitor for type II diabetes (co-development with Banyu Pharmaceutical Co., Ltd.)  
Phase III / Combination therapy with insulin for type II diabetes (co-development with Banyu Pharmaceutical Co., Ltd.)

*Corebata® for Injection*  
*Corebata®* is a candidate for the trade name of a low-dose formulation of *Onoact® Injection*.  
**Japan:** J-NDA filed / Improvement of image quality of coronary arteries for coronary CT angiography

*Emend® Capsules*  
**Japan:** Phase III / Chemotherapy-induced nausea and vomiting in pediatric patients