

**We will accelerate R&D for next-generation core products, by further enhancing our new drug research and development capacity.**

Takeda has been engaged in achieving our goal to launch five new products onto the market during the five years from 2011 to 2015, by accelerating the challenge toward World Best Practice under the global research network.

## **TIKARAKOBU RESEARCH STRATEGY AND REFORM OF THE RESEARCH SYSTEM AND STRUCTURE**

Takeda positions lifestyle-related diseases, oncology and urological diseases (including gynecological disorders), central nervous system diseases (including bone and joint diseases) and gastroenterological diseases as the four core therapeutic areas and has been promoting efforts based on the Tikarakobu Research Strategy, by reestablishing research strategies geared toward achieving our goal of the 2006-2010 Medium-Term Management Plan.

The Tikarakobu Research Strategy aims to balance the "research resources concentration" and the "diversification of risk" by focusing and enriching the research themes in the strategy via the setting of drug categories which should be prioritized, and with the external environment, such as market and research trends, as well as the our strength, including the previous R&D achievements of the company, in mind.

Through this initiative, we devote all our resources to achieving the final



goal of launching new products onto the market, while effectively utilizing research resources and remaining prepared for any contingency. Furthermore, as for the reform of the research system and structure, we have introduced a structure capable of making clear decisions (stage-gate meeting) after clarifying the stage-gate criteria and covering all the obstacles in order to advance research themes. In addition, we have also been strengthening the multi-IND engine structure\*.

\*A structure to develop new drug candidates through friendly competition with several research bases, both at home and abroad. IND stands for Investigational New Drug application, meaning submission to the U.S. Food and Drug Administration (FDA) in order to conduct clinical trials on a new drug candidate. By further extension, IND means to develop new drug candidates.

## **ENHANCEMENT OF THE MULTI-IND ENGINES STRUCTURE**

Following Takeda San Diego, Inc. (TSD), which joined the Takeda group two years ago, Takeda has implemented the further enhancement of the multi-IND engines via the acquisition of Paradigm Therapeutics Ltd. (Cambridge, UK) and its subsidiary in Singapore and respectively



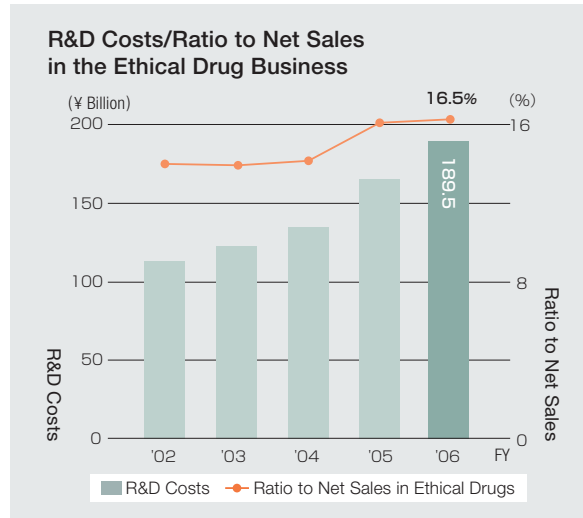
Pharmaceutical Research Div. (from left) Katsuya Sakimura, Yoshiaki Kassai, Yu Sako, Naoki Furuyama, Juran Kato and Naoto Inukai

renamed them Takeda Cambridge Limited (TCB) and Takeda Singapore Pte Limited (TSP), aiming to further enhance the multi-IND engine. Paradigm Therapeutics Ltd. was a bioventure established by researchers of the University of Cambridge in 1999. Paradigm has already developed a promising pipeline of novel drug discovery targets and compounds in key areas including pain, CNS disorders, prostate and breast cancer, diabetes, hyperlipidemia, and obesity as core therapeutic areas; many of which are fitting with Takeda's core therapeutic areas.

Following TSD with high-throughput protein crystallography technology, affiliating TCB and TSP which have world-class target identification and validation capabilities based on genetic engineering and animal model creation technology, as well as related phenotype analysis technologies, has further facilitated the establishment of a global research network with hubs in Japan, the U.S., Europe and Asia. We aim to advance and further improve the research infrastructure in order to collect information on cutting-edge scientific technologies promptly and flexibly apply such technologies, with a view to global cooperation with ventures having an edge in the areas of antibody drugs, oncology and CNS diseases, as well as future company acquisitions.

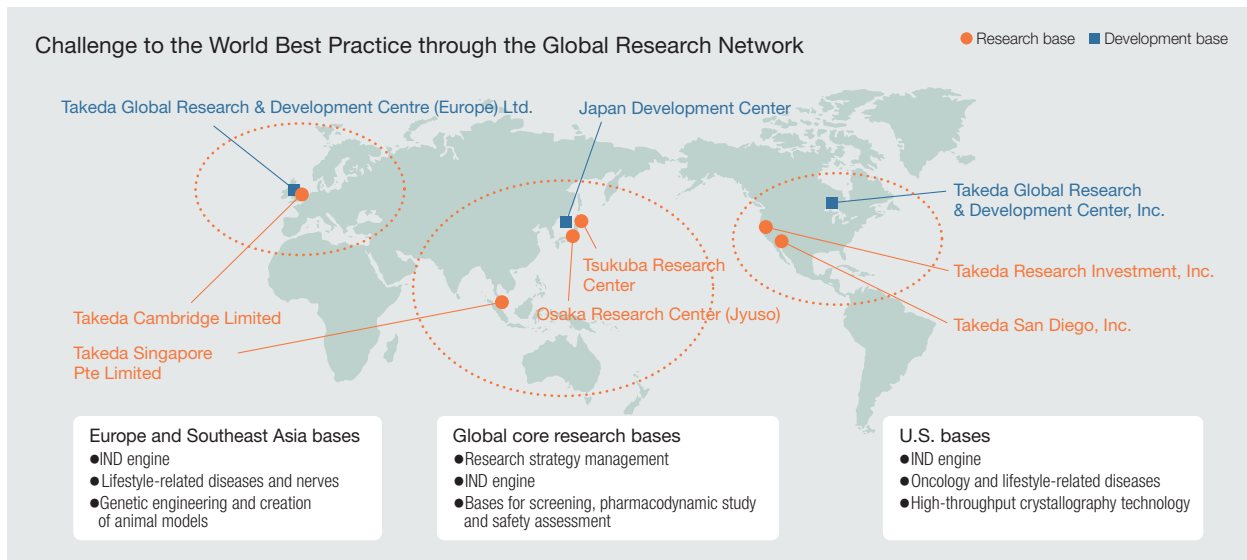


Takeda Cambridge Limited



### LAUNCH OF A NEW RESEARCH FACILITY IN JAPAN

In October 2006, Takeda made the decision to integrate the R&D function based in Osaka and Tsukuba, Ibaraki and launch a new R&D facility in Fujisawa, Kanagawa. Currently, we have been proceeding with further elements of the plan, with operational launch targeted for fiscal 2010. We aim to successfully conduct leading global research on drug discovery by establishing a vigorous and dynamic research structure, attractive to both in-house and external research institutes, as well as researchers, by unifying the domestic research base and launching a new research facility.



## R&D pipeline

Pipeline represents ethical drugs under development, from the start of research to approval/launching. The development of new drugs requires considerable time - more than ten years - and enormous expense.

Clinical trials are conducted on humans for drugs for which basic research and nonclinical tests have been already completed. Through the procedures of clinical trials in Phases I, II, and III and following efficacy and safety evaluation, the pipelines are launched onto the market as new drugs after approval by the regulatory authorities.

## Major Promising Pipelines as Next-generation Core Products

### ■ Anti-hypercholesteremia drug: TAK-475

TAK-475 is a squalene synthase inhibitor, discovered by Takeda. Due to its mechanism of action, which differs from previous statin drugs, a high treatment effect is expected with a combination therapy with existing anti-hyperlipidemia drugs, including statins, in addition to the monotherapy. Currently, Phase III clinical trials of TAK-475 are underway in the U.S. and Europe, and Phase II clinical trials are ongoing in Japan.

### ■ Anti-diabetic drug: SYR-322

SYR-322 is a promising pipeline for the treatment of diabetes, following our core product: *Actos*. SYR-322 was created by Takeda San Diego, Inc. (TSD) as a therapeutic agent for Type 2 diabetes, with a DPP-4\* inhibitory action. In Europe and the U.S., clinical trials for combination therapy are underway in addition to monotherapy. Likewise, in Japan, Phase II clinical trials for SYR-322 are being conducted.

\* An enzyme that degrades glucagon-like peptide-1 (GLP-1) - a hormone to stimulate the insulin secretion.

### ■ Anti-peptic ulcer drug: TAK-390MR

TAK-390MR is positioned as a successor product to lansoprazole, one of our mainstay products. TAK-390MR is a pipeline developed based on our own formulation technologies, as an enantiomer of lansoprazole, and can maintain the effective blood concentration for longer time. It is being developed by TAP Pharmaceutical Products Inc. (TAP), which has the expertise in the development of drugs for treatment of GERD. Currently, Phase III clinical trials in the U.S. are underway while the Phase I clinical stage has been completed in Japan.

| Development Code  | Generic Name               | Brand Name (Country/Region)  |
|---|----------------------------|--|
| <b>Franchise I : Lifestyle-Related Diseases</b>                               |                            |  |
| <b>TCV-116</b>  | Candesartan cilexetil      | <i>Blopress</i> (Japan, Europe, Asia)<br><i>Amias, Kenzen</i> , etc. (Europe)  |
| <b>AD-4833</b>  | Pioglitazone hydrochloride | <i>Actos</i> (Japan, U.S.A., Europe, Asia)<br><br><i>Actoplus Met XR</i> (U.S.A.)<br><i>Competact</i> (Europe)<br><i>Duetact</i> (U.S.A.)<br><i>Tandemact</i> (Europe) |
| <b>AO-128</b>   | Voglibose                  | <i>Basen</i> (Japan, Asia)   |
| <b>TAK-475</b>  | Not decided                |  |
| <b>TAK-428</b>  | Not decided                |  |
| <b>TAK-536</b>  | Not decided                |  |
| <b>LY333531</b>   | Ruboxistaurin              |  |
| <b>SYR-322</b>  | Not decided                |  |
| <b>ATL-962</b>  | Cetlistat                  |  |
| <b>TAK-583</b>  | Not decided                |  |
| <b>TAK-491</b>  | Not decided                |  |
| <b>SYR-472</b>  | Not decided                |  |
| <b>Franchise II : Oncology and Urological Diseases</b>                        |                            |  |
| <b>TAP-144-SR</b>   | Leuprorelin acetate        | <i>Leuplin</i> (Japan), <i>Lupron Depot</i> (U.S.A.)<br><i>Enantone</i> , etc. (Europe, Asia)  |
| <b>EMD72000</b>   | Matuzumab                  |  |
| <b>R-851</b>  | Not decided                |  |
| <b>AF37702</b>  | Not decided                | <i>Hematide</i> (U.S.A.)   |
| <b>Franchise III : Central Nervous System Diseases, Bone / Joint Diseases</b> |                            |  |
| <b>TAK-375</b>  | Ramelteon                  | <i>Rozerem</i> (U.S.A.)  |
| <b>NE-58095</b>   | Risedronate                | <i>Benet</i> (Japan)   |
| <b>Franchise IV : Gastroenterological Diseases</b>                            |                            |  |
| <b>AG-1749</b>  | Lansoprazole               | <i>Takepron</i> (Japan, Asia), <i>Prevacid</i> (U.S.A., Asia)<br><i>Ogast, Agopton, Lansox</i> , etc. (Europe)   |
| <b>TAK-242</b>  | Not decided                |  |
| <b>TAK-390MR</b>  | Not decided                |  |
| <b>SPI-0211</b>   | Lubiprostone               | <i>Amitiza</i> (U.S.A.)  |

| Drug Class                                 | Indication/Formulation   | Country/Region                                       | Stage of Development   |   |                           |                |                        |         |
|--|--|--|--|---|---------------------------|----------------|------------------------|---------|
|  |  |  | Phase I  | Phase II  | Phase III                 | NDA Submission | NDA Approval           |         |
| Angiotensin II receptor blocker            | Fixed combination with diuretic  | Japan<br>Europe                                      | ▶▶▶  | ▶▶▶   | ▶▶▶                       |                |                        |         |
|  | High doses   | Japan  | ▶▶▶  | ▶▶▶   | ▶▶▶                       |                |                        |         |
|  | Outcome study, DIRECT (Diabetic RETinopathy Candesartan Trial)   | Europe   | ▶▶▶  | ▶▶▶   | ▶▶▶                       |                |                        |         |
| Insulin resistance-improving drug          | Reduction of the risk of macrovascular events in patients with type 2 diabetes mellitus and pre-existing macrovascular disease (PROactive) | U.S.A.<br>Europe                                     | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2007.02 *<br>2007.01 * |         |
|  | Delay in progression of atherosclerosis  | U.S.A.   | ▶▶▶  | ▶▶▶   | ▶▶▶                       |                |                        |         |
|  | Combination drug of Actos/Metformin XT   | U.S.A.   | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2006.03                |         |
|  | Combination drug of Actos/Metformin  | Europe   | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2006.07                |         |
|  | Combination drug of Actos/SU   | U.S.A.<br>Europe                                     | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2006.07<br>2007.01     |         |
|  | Concomitant therapy with metformin   | Japan  | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2007.01                |         |
|  | Concomitant therapy with metformin and SU  | Europe   | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2006.10                |         |
|  | Concomitant therapy with insulin   | Japan  | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2007.06                |         |
|  | α-glucosidase inhibitor  | Impaired glucose tolerance (IGT)                     | Japan  | ▶▶▶   | ▶▶▶                       | ▶▶▶            |                        |         |
| Squalene synthase inhibitor                |  | Hyperlipidemia                                       | Japan<br>U.S.A.<br>Europe  | ▶▶▶   | ▶▶▶                       | ▶▶▶            |                        |         |
| Neurotrophic factor production accelerator | Diabetic neuropathy  | U.S.A.<br>Europe                                     | ▶▶▶  | ▶▶▶   |                           |                |                        |         |
|  |  | Angiotensin II receptor blocker                      | Hypertension   | Japan<br>U.S.A.<br>Europe                           | ▶▶▶                       | ▶▶▶            |                        |         |
| PKC β inhibitor                            | Diabetic maculopathy   | Japan  | ▶▶▶  | ▶▶▶   |                           |                |                        |         |
| DPP-4 inhibitor                            | Diabetic mellitus  | Japan<br>U.S.A.<br>Europe                            | ▶▶▶  | ▶▶▶   | ▶▶▶                       |                |                        |         |
|  |  | Lipase inhibitor                                     | Obesity  | Japan   | ▶▶▶                       | ▶▶▶            |                        |         |
|  |  |  | Neuropathic pain-improving drug                                      | Post-herpetic neuralgia                             | U.S.A.<br>Europe          | ▶▶▶            | ▶▶▶                    |         |
| Diabetic neuropathy                        | Japan<br>U.S.A.<br>Europe  | ▶▶▶  |  |   | ▶▶▶                       |                |                        |         |
| Angiotensin II receptor blocker            | Hypertension   | U.S.A.<br>Europe                                     |  | ▶▶▶   | ▶▶▶                       | ▶▶▶            |                        |         |
|  |  | DPP-4 inhibitor                                      | Diabetic mellitus  | U.S.A.<br>Europe                                    | ▶▶▶                       | ▶▶▶            |                        |         |
| LH-RH agonist                              | 6-month depot / prostate cancer  | Europe (Germany, Italy, France)                      | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2005.06/10/11          |         |
|  |  | Humanized monoclonal antibody against the human EGFR | Gastric cancer, non-small cell lung cancer, colorectal cancer        | Japan<br>U.S.A.<br>Europe                           | ▶▶▶                       | ▶▶▶            |                        |         |
| Immune response modifier                   | Human papillomavirus (HPV) infection   |  | U.S.A.<br>Europe   | ▶▶▶   | ▶▶▶                       |                |                        |         |
|  |  |  | Synthetic, peptide-based erythropoiesis-stimulating agent            | Chronic kidney disease (CKD), cancer-related anemia | Japan<br>U.S.A.<br>Europe | ▶▶▶            | ▶▶▶                    |         |
| MT1/MT2 receptor agonist                   | Insomnia   | Japan<br>Europe                                      |  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | ▶▶▶                    | 2007.03 |
|  |  | Circadian rhythm sleep disorder                      |  | U.S.A.  | ▶▶▶                       | ▶▶▶            |                        |         |
|  | Alzheimer's sleep/wake disturbance   | U.S.A.   | ▶▶▶  | ▶▶▶   |                           |                |                        |         |
|  |  | Bone resorption inhibitor                            | Once-a-week formulation  | Japan   | ▶▶▶                       | ▶▶▶            | ▶▶▶                    | ▶▶▶     |
| Paget's disease of bone                    | Japan  |  | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2007.07                |         |
| Proton pump inhibitor                      | Non-erosive reflux disease   | Japan  | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2006.06                |         |
|  | Injectable formulation : Upper gastrointestinal bleeding   | Japan  | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2006.10                |         |
|  | Secondary eradication of Helicobacter pylori   | Japan  | ▶▶▶  | ▶▶▶   | ▶▶▶                       | ▶▶▶            | 2006.08                |         |
|  | NSAID-induced ulcer  | Japan  | ▶▶▶  | ▶▶▶   | ▶▶▶                       |                |                        |         |
| TLR4 signal transduction inhibitor         | Severe sepsis  | Japan<br>U.S.A.<br>Europe                            | ▶▶▶  | ▶▶▶   | ▶▶▶                       |                |                        |         |
|  |  | Proton pump inhibitor                                | Erosive esophagitis and non-erosive gastro-esophageal reflux disease | Japan<br>U.S.A.                                     | ▶▶▶                       | ▶▶▶            | ▶▶▶                    |         |
|  |  |  | Chloride channel opener  | Constipation-predominant Irritable Bowel Syndrome   | U.S.A.                    | ▶▶▶            | ▶▶▶                    | ▶▶▶     |

\* The results from PROactives study were added into labeling.

## ENHANCEMENT OF THE DEVELOPMENT SYSTEM IN THE TRI-POLAR MARKETS (JAPAN, U.S., EUROPE)

Takeda has been accelerating the development of "core products in next generation" by integrated operation for clinical trials and improved structure toward the submission for marketing and manufacturing authorization under the close collaboration among Takeda Global Research & Development Center Inc., Ltd. (TGRD) in the U.S. and Europe and the headquarters in Japan. We also have been striving for the establishment of "simultaneous submission system in three regions" through integrated clinical development operation as one of our important strategic tasks.

The Product Strategy Team (PST), which consists of cross-divisional members, including Research, Development, Marketing and other divisions, is now set up at research phase to get involved in strate-

gic product planning from the early stage in order to promote the maximization of additional values for products.

## ENHANCEMENT OF THE R&D PIPELINE THROUGH IN-LICENSING AND ALLIANCE ACTIVITIES

Takeda positions in-licensing and alliance activities as important supplemental measures to enhance the R&D pipeline, and will continue to proactively work to accomplish this goal. In order to efficiently expand our activities at a global level, we have been implementing the development of its promotional structure, including the appointment of staff exclusively in charge of alliance and in-licensing activities in Japan, the U.S. and Europe and we have successfully achieved steady results in fiscal 2006 as shown below.

## Alliance Advances in In-Licensing and Alliance Activities from April 2006 Onwards

| Partners                               | Contents  |
|--|---|
| Sucampo Pharmaceuticals, Inc. (U.S.A.) | In April 2006, TPNA and Sucampo Pharmaceuticals jointly commenced the marketing of <i>Amitiza</i> , a treatment for chronic idiopathic constipation, discovered and developed by Sucampo Pharmaceuticals, in the United States.   |
| Cephalon, Inc. (U.S.A.)                | In June 2006, Cephalon, Inc. and Takeda Pharmaceuticals North America, Inc. entered into an agreement to co-promote <i>Provigil</i> tablets, an agent to promote wakefulness.   |
| Affymax, Inc. (U.S.A.)                 | In June 2006, Takeda entered into a license agreement for <i>Hematide</i> for the treatment of chronic kidney disease/cancer related anemia covering overseas markets. This allowed us to acquire exclusive global development and commercialization rights for the product, together with the license agreement concluded in February 2006, for the Japanese market. |
| Galaxy Biotech, LLC (U.S.A.)           | In July 2006, Takeda acquired an exclusive worldwide right from Galaxy to develop, manufacture and market the HuL2G7, a humanized antibody against hepatocellular growth factor related to mediate proliferation, metastasis and angiogenesis of many types of tumors.  |
| Xenon Pharmaceuticals Inc. (Canada)    | In September 2006, Takeda acquired exclusive development and marketing right for XEN401, which was discovered by Xenon and in currently in pre-clinical phase, for Japan and several Asian countries.   |
| XOMA Ltd. (U.S.A.)                     | In November 2006, XOMA and Takeda entered into a research and development collaboration agreement for discovery, development and manufacture of a therapeutic monoclonal antibody, and in February 2007, expanded the number of potential therapeutic antibody programs under the said collaboration scheme.  |
| 3M (U.S.A.)                            | In March 2007, 3M and Takeda entered into an agreement for Takeda to acquire the all rights to R-851 from 3M which was originally developed by 3M for topical cervical high-risk human papillomavirus (HPV) infection and cervical dysplasia.   |
| LG Life Sciences, Ltd. (Korea)         | In March 2007, LG Life Sciences and Takeda executed global licensing and research collaboration agreement to discover, develop and commercialize anti-obesity drugs.  |
| CanBas Co., Ltd. (Japan)               | In March 2007, CanBas and Takeda entered into a commercialization collaboration agreement for an investigational cancer treatment compound CBP501 and its backup compounds that were discovered and being developed by CanBas.  |
| BioWa, Inc. (U.S.A.)                   | In May 2007, Takeda was granted a non-exclusive right from BioWa for using BioWa's patented POTELLIGENT® Technology platform for preparing antibodies with enhanced antibody-dependent cellular cytotoxicity (ADCC).  |
| Archemix Corp. (U.S.A.)                | In June 2007, Archemix and Takeda entered into an agreement that focuses on the discovery, development and commercialization of first-in-class aptamer-based therapeutics.  |