R&D ACTIVITIES

Building Efficiency and Getting Results

Current research is split between two specific areas of expertise—new products based on our long pioneering involvement with Glycosaminoglycans (GAGs), a part of the broad spectrum of glycoconjugates, and development of novel products to serve a wider area of joint disease extending beyond, that now served by the ARTZ®-series products. With a keen sense of urgency, we have fortified our system for intensive timeline management.

We are also expanding our product pipeline through co-development and licensing activities while simultaneously accelerating in-house research and development programs. Our triple emphasis on in-house development, licensing and collaborative research and alliances with other institutions is the best way to assure a consistent launch of the new products that will bring profits to sustain further development and growth.

Seikagaku aims to pump 20% of net sales back into research and development, which is conducted by a staff of

Newly approved for use in Japan

“MucoUp® was approved by the Japanese Ministry of Health, Labour and Welfare (MHLW) in October 2006. Endoscopic mucosal resection is thought to be a minimum invasive operation. Compared with other types of surgery, it shortens hospital stays and reduces risk of long-term post-surgical complications.

The launch of MucoUp® is expected to promote endoscopic mucosal resection, to the benefit of patients, and reduce medical costs. We started negotiation with MHLW to decide the price for insurance reimbursement toward the early start of sales.”

Seikagaku has accumulated sizeable knowledge assets through its long involvement in the growing field of Glycoscience. This knowledge is the basis for development and supply of innovative pharmaceuticals and other products.

R&D Basic Policy and Structure

MucoUp® (SI-4404) Operating Aid for Endoscopic Mucosal Resection

By injecting SI-4404 as an operating aid into the sub-mucosal layer at the lesion of tumors in the gastrointestinal tract, the lesion rises to form a dome that can be more easily, safely and completely removed by endoscopic mucosal resection.
SI-6603 Treatment for Lumbar Disc Herniation

Chondroitinase ABC is a main ingredient of SI-6603 and a specific GAG degrading enzyme that is produced from bacteria. It dissolves/degrades chondroitin sulfate, dermatan sulfate and hyaluronic acid, the main components of nucleus pulposus in the disc. A single injection of SI-6603 into herniated lumbar disc is expected to show the same efficacy as surgical treatment, by reducing volume of nucleus pulposus in the disc.

“SI-6603 will not affect the surrounding tissues or organs of the disc such as blood vessels and nerves. SI-6603 is expected to be a highly safe drug for patients with lumbar disc herniation. In October 2005, we completed construction of an investigational drug substance production facility, based on the latest GMP* standards. We are now preparing for the next step, which is to conduct Phase II trials in Japan and the United States in spring 2007.”

*GMP means Good Manufacturing Practice—a production management and quality control standard for pharmaceuticals and quasi-drugs.

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179, or one-third of the total number of employees. This level is sufficient to sustain projects now under way and we are hiring more as needed to sustain our licensing and exploratory research.

In October 2006, MucoUp®, aid for endoscopic mucosal resection, was approved by the Ministry of Health, Labour and Welfare for use in Japan, and in September 2006, two themes were added to the pipeline:

- Cross-linked hyaluronate hydrogel, Gel-200, which entered directly into a Phase III clinical trial in the U.S.
- An adenosine A3 receptor agonist (A3AR Agonist) for the treatment of inflammatory diseases (excluding those of the eye), licensed from Can-Fite BioPharma Ltd. of Israel for development, manufacturing, sales and sub-licensing in Japan.

There are now four themes in our development pipeline. In addition to these themes, many more projects are currently at the pre-clinical trial stage. We anticipate announcing three projects as their clinical trials begin over the next one to two years.

At each milestone date in the development process, the Seikagaku Group carefully evaluates and judges its progress and, with stringent objectivity, selects themes for continued work.

Gel-200 entered directly into a Phase III clinical trial in the U.S. We aim to bring the product into the U.S. market within four years in addition to SUPARTZ®. It is expected that single-injection Gel-200 will also expand the treatment options for patients with knee osteoarthritis and strengthen the competitiveness of Seikagaku-brand products in winning market share in the U.S. We hope for its early launch.”

Kenji Miyamoto
Section Manager
Chemistry Department
Central Research Laboratories

Mine Higuchi
Senior Staff
Formulation Department
Central Research Laboratories

Gel-200 was recently added to our development pipeline. In September 2006, a Phase III clinical trial was started in the United States for this medical device. We aim to bring the product into the U.S. market within four years in addition to SUPARTZ®. It is expected that single-injection Gel-200 will also expand the treatment options for patients with knee osteoarthritis and strengthen the competitiveness of Seikagaku-brand products in winning market share in the U.S. We hope for its early launch.”

Gel-200 is a medical device for the treatment of osteoarthritis of the knees by single injection into a joint. The main ingredient is cross-linked hyaluronate hydrogel manufactured using exclusive cross-linking technology. It possesses extremely high viscoelasticity, which allows it to remain in the knee-joint cavity for long periods. The single injection is expected to give long-term pain relief, which is ideal for the U.S. market, where patients and physicians prefer a lower frequency of joint injections.
"This is a low-molecular-weight compound under development by the licensor, Can-Fite BioPharma. Can-Fite BioPharma is currently conducting Phase IIb clinical trials in the U.S., Europe and Israel. The results from clinical trials conducted to date have demonstrated promising efficacy as monotherapy in patients with rheumatoid arthritis. Seikagaku intends to develop the drug primarily for the treatment of rheumatoid arthritis, and expects to commence Phase I clinical trials in Japan in 2008."

Pipeline update: In 2006, Gel-200 entered into a Phase III clinical trial and we licensed-in A3AR Agonist, currently in pre-clinical development in Japan. In accordance with our project evaluation policy, we withdrew from a joint development project relating to an NF-κB decoy oligonucleotide product, and terminated an option agreement for the right to in-license an anti-psoriasis drug (CB-12181 owned by Carma Biosciences).

**PIPELINE**

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Market size: $\subseteq$ Large: ¥10 billion or higher $\subseteq$ Middle: ¥2~¥10 billion $\subseteq$ Small: Less than ¥2 billion *In the U.S. hyaluronate acid injection market, some sales overlap with existing SUPARTZ® sales.

"We have completed selection of human antibody types for development candidates. The license holder, BioTie, is expected to reinitiate a Phase I clinical trial overseas by spring 2007."

"This substance selectively stimulates the adenosine A3 receptor that is highly expressed in pathological inflammatory cells. By its agonistic effect on the adenosine A3 receptor, it modulates cellular signal transduction, which plays an important role in the pathogenesis of inflammation, and suppresses production of inflammatory cytokines such as TNF-\(\alpha\), IL-1 and IL-6. It is expected that the drug will be widely accepted as an anti-inflammatory drug given this novel mechanism of action and preferential safety profile.

**SI-3106**

Anti-VAP-1 Antibodies for Suppression of Inflammation (In-license from BioTie Therapies Corp.)

As per the license agreement, Seikagaku is carrying out the development of this drug. Conventional anti-inflammatory drugs suppress the generation of or inhibit proinflammatory substances, but this product acts on the VAP-I (vascular adhesive protein 1) that mediates adhesion of leukocytes to the endothelium of blood vessels and their infiltration into the site of inflammation. Therefore, it will be a novel anti-inflammatory drug with its unique mode of action.

**A3AR Agonist**

Adenosine A3 Receptor Agonist for Inflammatory Diseases (In-license from Can-Fite BioPharma Ltd.)

This substance selectively stimulates the adenosine A3 receptor that is highly expressed in pathological inflammatory cells. By its agonistic effect on the adenosine A3 receptor, it modulates cellular signal transduction, which plays an important role in the pathogenesis of inflammation, and suppresses production of inflammatory cytokines such as TNF-\(\alpha\), IL-1 and IL-6. It is expected that the drug will be widely accepted as an anti-inflammatory drug given this novel mechanism of action and preferential safety profile.