Japan’s Bioventures Today —
Immuno-Biological Laboratories Co., Ltd.

* This article is contributed by JAIC Asia Holdings Pte. Ltd. as a part of a collaboration with World Scientific Publishing Co., Pte. Ltd.

IBL's Background

Immuno-Biological Laboratories Co., Ltd. (“IBL”) is a well-established bioventure company with a history of more than 20 years. Founded in September 1982, IBL has been focusing on the research and development of antibodies against proteins related to cancers, inflammation, and brain and nervous system disorders. Mr Tsutomu Seito, the founder and president of IBL, plays a key role in the success of IBL. Mr Seito’s wide network gained through his 11-year career at National Cancer Center Research Institute, a three-year career at Niigata University, Faculty of Medicine, and his working experience in a private firm, Japan Immunoresearch Laboratories Co., Ltd., a medical device and diagnostic reagent company, has contributed greatly to the growth of IBL.

IBL's Business

Based on its expertise and technologies gained over 20 years of research, IBL currently focuses on three areas: antibody-based products, laboratory animals, and contract research services.

1. Antibody-based Products

IBL’s core products are the antibody-based products, particularly the reagents for research use. These reagents are often used to detect, identify, separate, and purify proteins in life science research. IBL possesses approximately 800 kinds of antibody-based reagents that identify various proteins, including amyloid β protein, a protein which often appears in the brain of Alzheimer's disease patients, and leptin, a protein which is related to obesity and diabetes. Approximately 80.5% of these reagents are developed in-house, while the rest are licensed from other companies.

The major in-house reagents include the following:

**ERC/Mesothelin Assay Kit**

IBL has successfully commercialized “Human N-ERC/Mesothelin Assay Kit – IBL,” and started marketing the product in Japan for research use in June 2006. This kit detects “ERC/Mesothelin,” a type of protein secreted by mesothelial tumor cells. This kit uses IBL’s proprietary antibodies that attach only to mesothelin. Currently, computerized tomography is used to detect mesothelial tumors; however, it can only detect the tumor at its late stage. Thus, this revolutionary kit is gaining industry attention as a method to detect mesothelial tumors at an earlier stage. This kit will be used at Juntendo University Hospital’s asbestos outpatient unit which was established in August 2005 to provide medical services for patients with illnesses caused by the inhalation of asbestos.
Industry Watch

**c-Kit (Receptor Tyrosine Kinase) Antibody**
This antibody detects c-Kit tyrosine kinase, which is often expressed in gastrointestinal stromal tumor (GIST) patients. Gleevec/Glivec™, a medicine developed by Novartis that inhibits c-Kit tyrosine kinase, shows great efficacy against chronic myelogenous leukemia and GIST. However, Gleevec/Glivec™ is only administered to GIST patients who express c-Kit tyrosine kinase, and thus this kit is used before the treatment.

In March 2006, IBL signed an agreement with Copenhagen-based Dako A/S to supply c-Kit antibody, CD117, exclusively. CD117 is an important component of Dako’s c-Kit pharmDx™ test, which has been approved by the US Food and Drug Administration (FDA) to be used as a kit to identify GIST. It is also suitable for treatment with Gleevec/Glivec™ developed by Novartis.

**Human Osteopontin Assay Kit**
Osteopontin is a bone matrix protein found in milk, placenta, urine, leukocyte kidney and some tumor tissues. It is known to have various functions including the regulation of immunological systems, especially the regulation of bone resorption in osteoclast cells. Over-function of osteopontin causes excess osteoclastic activities and inflammation, thus often resulting in the development of rheumatoid arthritis. Osteopontin is also believed to be associated with various bone diseases and cancer metastasis. This kit can be used for the monitoring of rheumatoid arthritis patients during treatment and also for the diagnosis of clinical conditions.

Given the fact that antibody-based products are accepted now, not only for reagents, but also for diagnostic products and for drugs, IBL has expanded its business into diagnostic products and therapeutics using its technology to produce various antibodies.

For diagnostic products, IBL currently has one in-licensed product called Targocid TDM Kit.

**Targocid TDM Kit**
Targocid (Teicoplanin) is a glycopeptide antibiotic which is particularly effective for *methicillin-resistant staphylococcus aureus* (MRSA). It is essential to monitor the concentration of targcocid in the blood in order to ensure its effectiveness and safety. This kit uses a technology called fluorescence polarization immunoassay (FPIA) to measure targcocid concentration in the blood within a short time.

For antibody-based therapeutics, IBL is currently developing the following:

**Anti-Osteopontin Antibody**
Joint studies conducted by IBL and Professor Toshimitsu Uede from the Institute for Genetic Medicine of Hokkaido University have successfully produced an antibody called 2K1, which neutralizes osteopontin’s functions. A subsequent study jointly conducted by Hokkaido University, former Fujisawa Pharmaceutical Co. Ltd., and IBL has revealed that the 2K1 antibody has high potential to be developed into a drug.
Based on this finding, IBL and Astellas Pharma Inc. ("Astellas"), a Japanese pharmaceutical giant, have concluded a worldwide licensing agreement which grants Astellas the exclusive rights to develop, manufacture, and market anti-human osteopontin antibodies including 2K1 for therapeutic use in March 2006. Currently, Astellas and the Chemo-Sero-Therapeutic Research Institute are preparing clinical studies to humanize 2K1 with an aim to commercialize the drug by 2012.

**Anti-CEA Antibody**
Carcinoembryonic antigen (CEA) is a protein found in human colorectal cancer. The amount of CEA expression increases upon the onset of adenocarcinoma cancer and also when adenocarcinoma cancer spreads to the liver. Therefore, it is one of the most useful tumor markers and is often used during postsurgical tests. As IBL's anti-CEA antibody has superior specificity and bonding, it has high potential to be developed into an in vitro diagnosis and into a vector for missile therapy. In addition, IBL has successfully converted the antibody to harmless structure to human bodies and is developing it for a possible antibody-based drug.

**Anti-Amyloid β Antibody**
In Alzheimer's disease patients, unusually phosphorylated tau proteins accumulate inside the nerve cells in addition to deposition of the amyloid β proteins in the brain. Most of these amyloid β proteins are amyloid β 40 and amyloid β 42 cleaved from amyloid precursor proteins by β and γ secretases. There is a growing demand for assay systems globally as an accurate assay for each of these proteins is essential for basic research and drug development. IBL provides these systems while simultaneously pursuing the development of new drugs using specific anti-amyloid β antibodies.

2. **Laboratory Animals**
IBL distributes disease-model animals that are genetically modified and carry human pathologic conditions for use in basic medical research and drug development. IBL has been a distributor in Japan for Taconic Inc., the leading breeder of model animals for laboratory use in the US. In order to expand its business, IBL has obtained a license from Taconic Inc. and has started the production of the disease-model animals. Furthermore, IBL develops various original genetically modified mice.

3. **Contract Research Service**
Based on its technologies and expertise in immunology and cell research field, IBL provides contract research services to universities, medical institutes and researchers in pharmaceutical companies, among others. Its services include the production and purification of antibodies, gene transfer, as well as mass cultivation and maintenance of cells.

**Market Overview for Antibody-based Reagents and Diagnostics in Japan**
According to some industry sources, Japan's current market for antibody-based reagents is estimated at more than 4 billion yen. As the market for each product is relatively small, it is generally essential for companies in this industry to sell a wide variety of products.
However, some products with an annual sale of more than 10 million yen have emerged in recent years, and so the quality rather than quantity of the products is starting to recover more emphasis.

According to “Nikkei Bio Nenkan 2006” published by Nikkei Business Publications, Inc., Japan’s domestic market for monoclonal antibody-based in vitro diagnostics was approximately 88 billion yen in 2004. The market for such diagnostics in 2005 is expected to be around 90 billion yen, with only a slight increase as few novel products are being developed in recent years. On the other hand, the demand for the new type of diagnostics for customized medicine is showing a noticeable increase. More specifically, antibodies which recognize glycosylation are gaining the industry’s attention as the relationship between glycosylation and diseases is being unraveled.

**IBL’s Future**

IBL, with its antibody production technologies as its key technologies, aims to further expand its product lines. With the licensing agreement with Astellas for anti-human osteopontin antibodies and the collaboration with Juntendo University Hospital for the ERC/Mesothelin Assay Kit as important milestones, IBL is expected to play an important role in the antibody-based reagents, diagnostics, and drug field.

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