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Singapore Grooms Firms for Success

Scientific Expertise and Supportive Government Regulations

Robert Yuan, Ph.D., and
Thomas Haun

As executives, investors, and scientists make the long trek to Asia, the central question is, why?

“The drug markets in the West are mature and slow growing. The growth is in Asia and we need to be close to these emerging markets,” responded a senior executive at **GlaxoSmithKline** (GSK; London), a major pharmaceutical multinational with a large presence in Asia.

“But perhaps more importantly, this is where the action is. We can put together the facilities and teams in a high energy environment and make things happen faster there than anywhere else.”

Major multinationals have been expanding their activities to include applied research and clinical trials. These initiatives have been fueled by investment opportunities and liberal government.

New biotech companies start out with



S*Bio is a drug discovery company focused on cancer therapeutics.

three major decisions to make: how to find a realistic business model, a source of investors, and a location. Singapore's economic development policies have been designed to attract Western style high-tech companies.

In June 2000, Singapore's Economic Development Board (EDB) and **Chiron** (Emeryville, CA) established **S*Bio Pte Ltd.**,

a fully integrated drug discovery company directed toward cancer therapeutics.

S*Bio began operations in January 2002, with access to Chiron's collection of chemicals and validated targets, and gene expression data base. S*Bio has agreements with fifteen different organizations, thus gaining access to a total of 200,000 compounds.

MerLion's Key Agreements

Company	Country	Primary business	Secondary business
Athelas	Switzerland	Bacterial infections	Virulence targets
British Biotech	U.K.	Bacterial infections	Ribosomal assays
Fujisawa	Japan	Multiple diseases	
Genetic Therapeutics	U.S.	Virulence targets	
NovImmune	Switzerland	Immune disorders (e.g., type 1 diabetes) Immune targets	
Merck	U.S.	Infectious diseases	
Schering-Plough	U.S.	Multiple diseases	

Chiron also provided technology and training for S*Bio's staff. In return, Chiron has rights of first refusal for any new products, but S*Bio retains the right to accept a higher bid from another company.

At present, S*Bio has focused on two target classes: Sbio100 which blocks chromatin modifying enzymes (e.g., acetylases), and Sbio300, which acts on kinases that influence the cell cycle. Sbio101 is a histidine deacetylase which, with excess activity, leads to the turning off of normal genes. The corporate strategy is to generate one pre-development candidate compound per year.

Key Attractions

The business model of S*Bio is not uncommon, but its choice of a location is. Michael Entzeroth, Ph.D., CSO of S*Bio, provided insight into some of the key attractions of Singapore.

Bio One (a major venture capital fund) and Temasek Holdings (an investment arm of the Singapore government) are major investors in S*Bio. The company has developed close ties to the Genome Institute of Singapore, the National Cancer Center, NUS Oncology Research Institute and Johns Hopkins Singapore. These associations allow for validation of therapeutic targets as well as access to cancer expertise, while an agreement with **Shanghai Comman Pharmaceutical** provides expertise in chemical synthesis.

The island's existence as a major pharmaceutical manufacturing hub means

that senior industry executives travel there regularly, providing the opportunity for ongoing discussions. Government policy is highly supportive with strong patent protection, a favorable regulatory environment, and a good site for animal experiments.

Alternative Strategy

MerLion represents an alternative approach to the creation of a new biofirm. It was spun off in 2002 from the Center for Natural Products Research at the Institute of Molecular and Cell Biology (IMCB), which had received funding from GSK. It had a collection of lead compounds isolated in Southeast Asia plus GSK's collection of about 500,000 compounds. Its initial investment of \$13.5million came from GSK and EDB.

MerLion's principal weaknesses were the availability of screens and the need for chemical synthesis. Its strategy was to establish strategic alliances based on exclusive licensing of new drugs or joint ownership rather than the sale of services.

MerLion's agreements with biotech/drug companies provide access to proprietary technology and sharing of costs. Partner companies are responsible for both preclinical and clinical stages of drug development and subsequent production and marketing. In the case of smaller corporate partners, the sharing of risks is a major aspect of the agreements.

The first agreement was with Japan's

Fujisawa (Oksawa). A summary of MerLion's key agreements, which includes small biotech companies and large pharmaceutical multinationals, is shown in the *Table*.

A typical MerLion agreement is the one it has with **Schering-Plough** (Kenilworth, NJ). The Schering-Plough Research Institute (SPRI) is responsible for providing the assay technologies and MerLion will do the actual screening. Drug development is carried out by SPRI, which will get worldwide rights to any successful product.

MerLion will receive milestone payments, royalties from product sales, and rights to any drug candidates that are not pursued by Schering-Plough.

S*Bio and MerLion are drug discovery companies that have taken advantage of the scientific expertise and supportive governmental environment that are found in Singapore. However, it is the global debate on stem cells (particularly the U.S. prohibition on the use of government funding in the creation of new cell lines) that has created a rare opportunity.

Last September, the Singapore Parliament passed a bill on human cloning that prohibits the cloning of human embryos in humans or animals. It also forbids the development of human embryos outside a woman's body beyond 14 days. But the door has been opened for the development of stem cell lines for therapeutic purposes.

ES Cell International (ESI) was founded on research taking place between the National University of Singapore and Monash University (Australia).

Subsequently, intellectual property from the Hadassah University Hospital (Israel) and the Netherlands Institute of Developmental Biology came under the company's R&D umbrella. This brought together an important combination of technologies:

- NUS: growth conditions and scale-up

of existing and newly derived hES cells.

- Monash: directed differentiation and development of hematopoietic progenitors.
- Hadassah: development of dopaminergic neurons for treatment of Parkinson's and genetic modification of hES cells.
- Netherlands: development of heart cells from hES cells.

U.S. government stem cell policy accelerated the development of ESI, which was established in 2000 and now has additional facilities in Australia. It raised S\$17 million (US\$11 million) from Life Sciences Investments (part of EDB) and ES Cell Australia Ltd., an Australian investment group.

Robust Platform

ESI has focused on the creation of a robust platform that allows for the scale-up of hES cells and, specifically, differentiated cells, their stable transplantation into human patients, and the identification of the growth factors that are essential to the maintenance and differentiation of these stem cells.

The genes and their products can be developed as either growth factors or reagents to grow specifically differentiated cells for cell replacement therapies. Its first therapeutic application will be in the treatment of diabetes through the conversion of hES cells into islet cells. The company plans on beginning clinical trials in 2006.

Additional clinical applications involve neurology for the treatment of degenerative diseases (such as Parkinson's) and cardiology through the use of heart cells to repair damaged heart tissue resulting from myocardial infarction.

There is also an interest in hematopoiesis as an approach to the treatment of leukemia.

Development of hES cell lines would take place in Singapore along with scale-up production. Clinical trials would then be carried out in Singapore, the U.S., and Europe. Appropriate treatment centers would then be established where diagnosis, treatment and follow-up would take place.

Cordlife, a company founded in 2001 in Singapore, is another firm targeting stem cell technology. Cordlife's core business is the collection, processing, and storage of umbilical cord stem cells. This allows the transplanted cells to be perfectly matched to the patient.

In principle, there are some 72 diseases that could be treated through the transplantation of such cord stem cells. This does require an efficient and reproducible process for large scale production.

Cordlife took the route of merging with **Cytomatrix** (Cambridge, MA). The basic premise was that the optimal growth of mammalian cells required a 3-D orientation. Cytomatrix developed a carbon skeleton structure coated with metals at high temperature and functionally resembling bone marrow.

With support from EDB, this system is being used for the efficient growth of stem cells. The company is establishing a regional network of stem cell treatment centers. The Cambridge laboratories also are exploring alternative sources of stem cells (such as adipose tissue).

A-Bio Pharma was founded in 2002 as a spinoff from the Bioprocessing Technology Center. The company is a custom contract manufacturing entity dedicated to the production of biologicals, which includes biological therapeutics, mono-

clonal antibodies, and vaccines. A-Bio is fully owned by Bio-One, the EDB venture capital arm.

At present there are some 500 biological products that are going through the various stages of clinical trials. It is estimated that U.S. demand for biologicals will grow at an annual rate of 12%, reaching a market value of \$56 billion in 2006.

The design, construction and regulatory approval of production facilities for biologicals is lengthy, which is likely to lead to a shortage of biologicals manufacturing capacity worldwide. Contract manufacturing companies are expected to fill this gap.

A-Bio has a staff of ninety recruited from all over the world. Their current facility allows small-(up to 40 liters) and large-scale production (up to 500 liters). The current work focuses on maximizing cell culture growth and development.

A-Bio provides process development, production of clinical lots, analysis, and regulatory counseling. A-Bio plans to expand into a new facility that will house two 500-liter bioreactors.

One important milestone in this plan is the signing of an agreement with GSK Biologicals for the development and manufacture of clinical lots of GSK's promising new vaccines.

The past five years have seen the creation of a number of innovative biotech firms. All of them have been led by expatriates who have made a conscious decision to establish themselves in this island state.

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Robert Yuan, Ph.D., is a professor of cell biology and molecular genetics at the University of Maryland in College Park (email: ry11@umail.umd.edu). Thomas Haun is a senior in the honors program at the University of Maryland.