Singapore: An Emerging Leader in Biomedical Sciences

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With a heavy investment in biomedical research — particularly the $330 million to build Biopolis in 2003 — Singapore is seeing the fruits of its labor blossom.

While New York City is commonly referred to as the financial capital of the world, Singapore is rapidly becoming known as the biomedical sciences capital of the world. Singapore's establishment of Biopolis has put it on the map as the epicenter for the biomedical sciences industry (Figure 1). An integrated complex with 2.4 million ft^2 of space, Biopolis is home to six public research institutes of the nation's Agency for Science, Technology and Research (A*STAR) — the BioInformatics Institute (BII); the Bioprocessing Technology Institute (BTI); the Genome Institute of Singapore (GIS); the Institute of Bioengineering & Nanotechnology (IBN); the Institute of Medical Biology (IMB); and the Institute of Molecular and Cell Biology (IMCB) — with a seventh institute (Singapore Institute for Clinical Sciences (SICS)) nearby. Alongside these institutes are several private-sector R&D laboratories, including the Novartis Institute for Tropical Diseases and GSK Cognition and Neurodegeneration Center. Biopolis is equipped with state-of the-art scientific resources and services, such as flow cytometry, mass spectrometry, bioimaging and specific pathogen free animal facilities.

"Biopolis represents a vision to establish the entire value chain of biomedical sciences activities in Singapore — from research and development to manufacturing and healthcare delivery. In doing so, the biomedical sciences industry will generate economic wealth for Singapore, create jobs for our people and improve human health and quality of life," said Tony Tan Keng Yam, deputy prime minister and coordinating minister for security and defense at the official launch of Biopolis. As anticipated, the impact of Biopolis has been tremendous. Before Biopolis opened,

Figure 1. Opened in 2003, Biopolis, the epicenter of biomedical R&D in Singapore, currently has 2.4 million ft^2 of space.

the manufacturing output for the biomedical sciences industry was $6.4 billion. The latest data indicate that this figure has more than doubled to $15.2 billion.

Bioprocessing activities

The BTI (Figure 2) has dual roles of pursuing cutting-edge bioprocess research leading to technologies that impact biomedical science and biomanufacturing, as well as nurturing talents for the scientific community and industry. BTI partners the universities and polytechnics in Singapore to develop a solid workforce for the biologics industry. True to its mission, over 400 students have completed bioprocess modules, undertaken undergraduate attachment or PhD research at BTI in the past five years.

To attract talented individuals, BTI established the Bioprocess Internship Programme (BIP) in 2005. The program consists of six months of intensive research, coupled with six months of structured training in expression

engineering, cell culture, downstream processes, analytical techniques and GMP. BTI has also been supporting overseas attachment programs (sponsored by the Singapore Economic Development Board), where graduates spend up to 18 months in biologics companies, and return to work in Singapore after their specialized training.

Many R&D achievements have already been attained by BTI. In particular, the institute has developed capabilities in: the production of biotherapeutics from animal and microbial cells; and the expansion of human embryonic stem cells (hESC) for cellular therapeutics. BTI is divided into several groups as discussed below.

Figure 2. In addition to R&D break throughs, the Bioprocessing Technology Institute is tasked with the goal of nurturing talented individuals.

The Expression Engineering group has been generating novel host cell lines that lead to the production of high quality biotherapeutics at high yield. Chinese hamster ovary (CHO) mutants have been isolated with defects in the apoptosis and glycosylation pathways, which can be used as robust host cell lines for biotherapeutic (recombinant protein) production. Several proteins regulating recombinant protein production at the transcription or translation level have also been identified, which are interesting targets for increasing productivity.

The Animal Cell Technology (ACT) and Microbial Fermentation groups develop strategies to enhance recombinant protein yield in mammalian and microbial cell cultures, respectively. The ACT group has developed proprietary protein-free chemically defined media for the cultivation of CHO, 293-HEK and hybridoma cells. A dynamic on-line feeding strategy based on low glutamine has led to 10-fold improvement in recombinant protein yields (*1*). The advent of '-omic' technologies has created new avenues for more insightful studies of mammalian cells producing recombinant proteins. In one study, novel CHO gene targeted (GT) cell lines were created by manipulating early apoptosis signaling genes which were activated during fed-batch cultures, leading to increased cell densities; as well as improved yield and quality of the recombinant protein produced (*2*). BTI has co-developed the CHO chip with the University of Minnesota, creating a useful tool to understand the physiology of the cells during recombinant protein production. This has subsequently led to the formation of the Consortium for CHO Cell Genomics in 2006 under the auspices of the Society of Biological Engineering.

In the Microbial Fermentation group, microarray, proteomic and metabolomic studies have helped to design strategies to direct cellular resources towards secondary metabolite production in *Actinomycetes* and plasmid production in *E coli*. Expertise developed through the handling of these systems is currently being applied to study antibody fragment production in *E coli*.

The Stem Cell group generates technologies for the characterization and large-scale production of hESC as cellular therapeutics. Culture platforms, which have been developed for long term expansion of hESC, include immortal mouse and human feeders (*3*) and serum-free, feeder-free cultures (*4*). Antibodies were raised against hESC that can be used to characterize, purify and remove undifferentiated hESC from cultures that have undergone differentiation. One of these proprietary antibodies has specific and quick cytotoxic activity against hESC.

BTI's efforts to support the biologics industry with research and workforce development have become increasingly relevant, with four major biologics investments being committed by Lonza, Genentech and GSK Biologicals in Singapore recently. Maintaining a pipeline of specialized workforce and developing strategic areas of bioprocess research will continue to be important charters for BTI. CEP

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