Bioprocessing Technology Institute

The Bioprocessing Technology Institute (BTI) is a national institute funded by the Agency for Science, Technology and Research (A*STAR) through its Biomedical Research Council. BTI spearheads bioprocess science and engineering research by combining molecular biology, biochemistry, proteomic and genomic sciences, to understand how to enhance the productivity of cells, develop better cell culture, fermentation and separation processes to manufacture important molecules such as antibodies, recombinant DNA and proteins that target a myriad of diseases. To advance cell-based therapeutics with human embryonic stem cells (hESC), we are developing serum free, feeder free culture conditions, novel antibodies to characterize them and high density culture systems. Creating a vibrant technology base while training a cadre of resourceful talents, BTI also engages in research collaborations leading to proprietary technologies with local and overseas companies and universities. Current strategic areas of research are:

- Expression Engineering
- Animal Cell Technology
- Microbial Fermentation
- Stem Cell Research
- Downstream Processing & Analytics
- Microarray and Proteomics Laboratories

We highlight three of research which include the development of High OutpuT cell lines, novel antibodies to human embryonic stem cells and an industrial collaboration with a US biotech company, Microbia.

High OutpuT (HOT) cell lines

BTI’s objectives are to improve bioprocessing science, cell culture and separation methods to enhance the ability of cells to produce antibodies and recombinant proteins. Apoptosis in such cultures leads to a drastic reduction in yield from such cells, and can even affect the quality of proteins produced from them. These proteins have many potential uses including medical treatment applications, and as such, there is a genuine need for a form of “apoptosis suppression” of industrial cell lines to exploit them as “protein production factories”.

BTI has identified four genes which affect the viability of cells in culture. Programmed cell death, or apoptosis, is a controlled process of cellular suicide, and is determined by age, cell health and culture conditions. In contrast to necrosis, cell death resulting from acute injury, apoptosis does not damage surrounding cells by exploding and releasing damaging internal components. Although apoptosis is not hazardous to surrounding cells, it is still an unwanted feature for researchers attempting to build up cells in culture.
BTI has engineered High Output (HOT) cells, which are designed to prevent the problem of apoptosis in cell culture and enhance the quantity and quality of products derived from the bioprocess. These HOT cells are engineered from Chinese Hamster Ovary (CHO) cells, which are commonly used by BTI and other groups to produce many types of antibodies and recombinant proteins including interferon gamma IFN, used in the medical industry for its antiviral and anti-tumor properties.

First, the team at BTI had to identify genes which were targets of apoptosis-causing proteins. To do this, the team used CHO cDNA microarrays to track apoptosis at different stages of a fed-batch culture of these cells. The researchers found potential ‘key targets’ of apoptosis suppression, and with this knowledge, constructed 4 CHO Gene Targeted (GT) cell lines, in which certain genes were suppressed.

Further work with these CHO GT cells showed that these cell lines were apoptosis resistant, and could achieve much higher cells densities in fed-batch culture as compared to the parental cell lines (9x10^6 cells/ml as opposed to 5x10^6 cells/ml in the parental cell lines). The yield of recombinant IFN in these GT lines was also shown to be 2.5 times higher, and the quality was not only excellent, but superior to that produced in non-GT CHO cell lines.

Novel antibodies to human embryonic stem cells

The Stem Cell Group has generated several new antibodies that recognize protein targets on human embryonic stem cells (hESC). The process began with the injection of live hESC into mice every week for 5 weeks. Blood serum was harvested and tested for the presence of antibodies against these foreign cells.
When there was an immune response, the mice were sacrificed and the B-cells which produce the antibodies from the spleen were harvested. After which these cells were fused with myeloma cells to make hybridomas. Culture supernatants from these hybridomas were then further tested for their ability to recognize three different hESC cell lines. Additional cell lines unrelated to hESC, such as mouse feeders, mouse embryonic stem cell lines and other human cell lines were tested as negative controls to ensure that the antibodies only recognize hESC. From this, 7 novel antibodies were identified and one of them is shown staining a hESC colony below.

Collaboration with Microbia on secondary metabolite production

A research collaboration between BTI, and Microbia Inc. (Boston, US) focuses on the development of metabolic engineering tools to improve the efficiency of secondary metabolite production from actinomycete bacteria. Actinomycetes produce a large number and a wide variety of antibiotics, antitumoral agents, insecticides and hydrolytic enzymes. Leveraging on Microbia’s association analysis-based technology platform, a combination of LC-MS/MS metabolite profiling and DNA microarray transcriptional profiling is used to identify genes with significant association to the production of specific metabolites. The initial target of the collaboration is to more efficiently produce a cytotoxic compound currently under clinical trials for use in cancer therapeutics. Longer term, the collaboration’s objective is to identify genes that facilitate rational strain improvement for a broad spectrum of pharmaceutical products made by actinomycete-related microbes.