

## **DEVELOPING INTEGRATED PLATFORMS FOR THE GENERATION OF CELL LINES EXPRESSING BISPECIFIC PROTEINS WITH DESIRED QUALITIES**

Jie Zhu, Cell Culture and Fermentation Sciences (CCFS)  
Lina Li, Judith Klover, Tom Albanetti, Michael Handlogten , CCFS  
Dengfeng Liu, Wai Keen Chung, Process Biochemistry and Purification  
Yariv Mazor, Antibody Discovery and Protein Engineering  
Diane Hatton and Raghavan Venkat, CCFS, MedImmune LLC

Key Words: bispecific protein, aggregation, mismatches and vector engineering

Complex bispecific and novel molecules are increasingly being developed as therapeutic proteins. These molecules present challenges for the generation of high quality manufacturing cell lines with good productivity and desirable product quality. High aggregation, poor sialylation and multiple chain mispairing are three of the major product quality problems affecting these molecules. To address these issues, we have developed a new expression platform which has been combined with high throughput analytical assays to screen and select clones with the preferred product quality profiles. Case studies will be presented on the development of cell lines expressing two types of bispecific molecules. To address the high level of aggregation observed with a bispecific molecule, the underlying cause of aggregation has been investigated and vector engineering tools have been applied to manipulate the expression of specific subunits of the protein leading to reduced aggregation. For another monomeric bispecific project, cell lines expressing four different polypeptides are generated and then efficiently screening at early stages of development to identify those with a high proportion of correctly assembled protein. These results also provide valuable information to assist in the molecular design and protein engineering of bispecific molecules.