# Preface

Since the introduction of recombinant human growth hormone and insulin a quarter century ago, protein therapeutics has greatly broadened the horizon of health care. Many patients suffering with life-threatening diseases or chronic dysfunctions, which were medically untreatable not long ago, can attest to the wonder these drugs have achieved. Although the first generation of protein therapeutics was produced in recombinant *Escherichia coli*, most recent products use mammalian cells as production hosts. Not long after the first production of recombinant proteins in *E. coli*, it was realized that the complex tasks of most post-translational modifications on proteins could only be efficiently carried out in mammalian cells. In the 1990s, we witnessed a rapid expansion of mammalian-cell-derived protein therapeutics, chiefly antibodies. In fact, it has been nearly a decade since the market value of mammalian-cell-derived protein therapeutics surpassed that of those produced from *E. coli*. A common characteristic of recent antibody products is the relatively large dose required for effective therapy, demanding larger quantities for the treatment of a given disease. This, coupled with the broadening repertoire of protein drugs, has rapidly expanded the quantity needed for clinical applications. The increasing demand for protein therapeutics has not been met exclusively by construction of new manufacturing plants and increasing total volume capacity. More importantly the productivity of cell culture processes has been driven upward by an order of magnitude in the past decade. For the biochemical engineering community, especially the researchers and bioprocess professionals engaged in cell culture engineering, this technological advancement is a cause for celebration.

Although the emergence of cell culture engineering is relatively recent, the demand for a robust manufacturing platform has propelled tremendous advances in a short decade. In the course of transforming from an exploratory technology to a robust instrument generating life-saving medicines, cell culture processes have evolved to almost uniformly employed stirred tank bioreactors for large-scale operations. Batch and simple continuous cultures are seldom employed, except on research scales. Fed-batch cultures and continuous processes with cell retention, also commonly referred to as perfusion culture, have become the norm. To capture the essence of those advances and to highlight products that have been the driving force for the expansion of cell culture

processes, three chapters in this volume are devoted to those topics: antibody products, fed-batch cultures and perfusion processes.

In the past decade, we have seen the specific productivity of recombinant antibodies by high-producing cells approach that of natural antibody secreting cells in vivo. This has been largely accomplished through random screening of clones with higher productivities. As we strive to generate hyper-producing cell lines that exceed the production capabilities of native antibody secretors in our bodies, screening processes will likely incorporate more rational approaches. Use of targeted markers, known to confer hyper-productivity traits will likely prevail. The complex trait of hyper-productivity is most probably a composite of many physiological characteristics, including robust growth, efficient energy generation, reduced susceptibility to reactive oxygen species, and enhanced protein processing and secretion machinery. Identifying the potential target genes for desired traits is a key to cell engineering. This issue also includes a chapter that gives a comprehensive review of the current state and future prospect of metabolic engineering of mammalian cells.

Looking to the future of cell culture engineering, we anticipate the productivity to continue to swing upward at a pace greatly exceeding the increasing demand to reduce the cost of goods. We are likely to see the next phase of process enhancement integrate renovations in process engineering with innovations in cellular engineering. Process renovations will continue to draw out the full capacity of fed-batch and perfusion processes. With imagination, one may see cell engineering efforts induce revolutionizing changes in cell culture processes. As genomic and proteomic tools become more readily available for cell culture engineering research and our understanding of the physiological basis of hyper-productivity further advances, such imagination will become closer to reality.

Minneapolis, July 2006 Wei-Shou Hu