Development of an Therapeutic Enzyme Iduronate-2-sulfatase for Treating Hunter Syndrome

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Iduronate-2-sulfatase(IDS) is one of the lysosomal enzymes involved in the degradation of heparan sulfate and dermatan sulfate. A deficiency in this enzyme results in accumulation these glycosaminoglycans in the lysosome and subsequently leads to the development of Hunter syndrome, a rare X-linked lysosomal storage disease in humans. Hunter syndrome can be treated by IDS therapy, gene therapy, or bone marrow transplant therapy. Among them, IDS therapy is known as the most promising method. IDS gene is cloned and inserted to CHO-DG44 cells. The cells with high copy numbers of expression vector were selected by gradual increase of MTX concentration. The recombinant CHO-DG44 cells were adapted to suspension culture for simple operation and easy scale-up of cell culture system. The serum free medium was developed by supplementing Dulbecco's modified eagle medium (DMEM) with a number of components which were shown to benefit the cell growth. The positive effect components for cell growth were identified by adopting a Plackett-Burman statistical design. The optimum concentrations of positive effect components were selected by using a response surface method. Finally, a formula of a low-protein serum-free medium for suspension culture of rCHO cells was developed. Optimum operation mode were searched by trying batch, fed-batch, and perfusion culture for the economical production of IDS. Anti-apoptotic agents and sodium butyrate were fed to media in order to increase the specific productivity of IDS in suspension culture of rCHO cells. Automatic control system was established based on the on-line monitoring by chemical analyser. The evaluation method of oxygen transfer coefficient was established for scale-up. The IDS isolation and purification process was also established based on affinity chromatography. Finally IDS Knock-out mouse is being constructed for clinical tests.