Firm on Quest to Improve Biomanufacturing

AmProtein Hopes that Its Novel Tools Will Change the Way Biomolecules Are Produced

Carol Potera

Founded by Matthew Hui, M.D., Ph.D., in 2002, **AmProtein** (www.amprotein.com) refers to itself as a "biotechnology powerhouse that wants to revolutionize the way the industry produces biomolecules." The company has locations in Hangzhou, China, and Camarillo, CA.

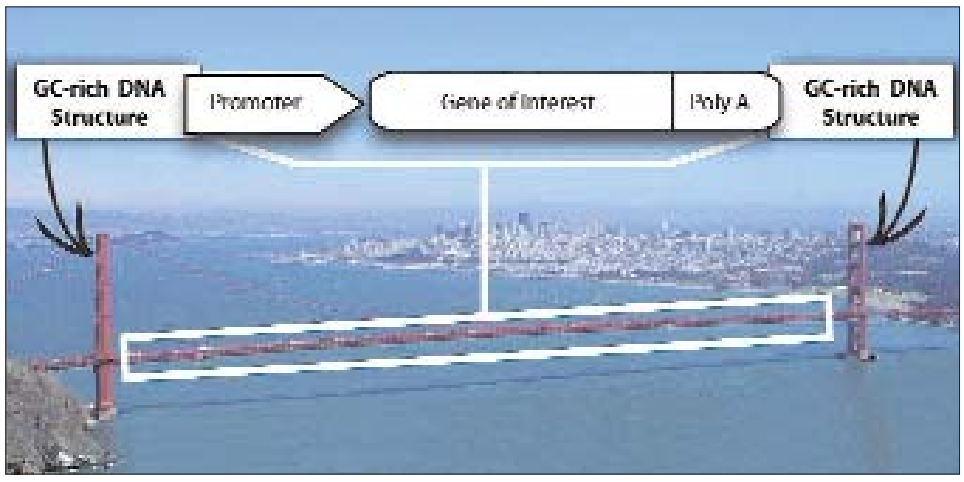
AmProtein has discovered a new vector system that stimulates mammalian cells to express proteins at commercial levels after just a few gene transfections. In addition, researchers at AmProtein have invented a disposable bioreactor that allows cells to grow in special plastic bags and obtain oxygen from ambient air.

Oxygen Transfer Method

Traditional bioreactors mix solutions of cells with rotating blades and push in air with bubbles (sparging), similar to a fish tank. But the shear force of the blades and even the bubbles, once they burst, damage delicate mammalian cells. An alternative technology now in use eliminates the blades by rocking plastic bags attached to a board, but this method is also mechanically inefficient.

Dr. Hui and his team devised a better method based on plastic bags that shake the cells in culture media. The swaying contents roll up the sides of the plastic bags, allowing cells to acquire oxygen in the process. The magic ingredient is a special type of plastic that is covered with microscopic dimples on the surface that attract oxygen from ambient air. The repetitive washings trap oxygen in the form of dissolved microscopic bubbles, which do not damage mammalian cells.

The Current Perfusion Bioreactor line (5 L, 50 L, and 150 L) is a high-density cell culture system for protein and antibody production and, alternatively, carrier-attached cells for vaccine production.



The GC rich segments act in a similar fashion to bridge towers. As bridge towers hold up a segment of road so the vehicles ma travel across a body of water, the structurally rigid GC-rich segments support the opening of chromatin, this exposing the promoter/enhancer regions to transcriptional factors and DNA binding proteins.

This dissolved oxygen transfer method is the underlying technology behind a line of patented bioreactors, including suspension and perfusion bioreactors. The bioreactor product line, named Current, ranges in size from 20 mL to 300 L. Current bioreactors offer a high-density cell culture system for protein and antibody production and vaccine manufacturing. The ready-to-use plastic bags come in sizes to fit different Current bioreactors.

AmProtein also sells single-use, plastic miniature shaking and rolling bioreactor systems that are ideal for studying early-stage process development. The mini-bioreactor vessels hold volumes of 20, 40, 150 mL, 1 L, and 2 L and up to 15 of the bottles fit into a mini-bioreactor. All of the company's bioreactors can be used for growing high-density CHO cell suspension cultures, as well as vaccine manufacturing cell lines, such as Vero, MDCK, and EPC cells. "The platform is scalable from bench to manufacturing and makes existing industrial bioreactors obsolete," says Dr. Hui.

AmProtein scientists are working to improve the bioreactors by developing biodegradable, or green, plastic containers. If successful, "this will be a first for the biotechnology industry," says Aziz Joudi, executive business associate. The researchers are experimenting with bacterial fermentation by *E. coli* to generate the biodegradable plastic, which shows good oxygen transfer properties.

GC-Rich Method

The bioreactors are used to improve the production of biotherapeutics in mammalian cells lines. In the past, bacteria like *E. coli* served as biological factories. Although yields are high for small biomolecules, it is difficult to manufacture large proteins with the proper structure and functional side groups in bacteria. "The majority of approved, marketed biotherapeutics are presently made in mammalian cells," says Dr. Hui. CHO and other mammalian cell lines, however, grow slowly and generate low yields of biomolecules.

Dr. Hui discovered an expression vector

series pMH 3-5, that speeds production rates and raises yields in CHO cells close to that of *E. coli* biomanufacturing. The vector is extremely rich in GC base pairs that appear to open chromatin structures.

About 99% of the chromatin in eukaryotic cells is condensed, and the vector acts like a chromatin-opening tool that exposes genes to transcription factors, thereby, promoting gene transcription. The GC-rich fragment is inserted at the 5' and/or 3' flanking region of the gene of interest. Once it is transferred to the cell nucleus, "it works so well that you can't stop it," explains Dr. Hui. "For example, we have produced generic hyper-glycosylated erythropoietin in CHO cells in 24 hours with the vector."

AmProtein researchers have used the vector to express 20 recombinant proteins and antibodies. The system achieves protein-expression levels of 50 to 120 picograms per cell per day for larger proteins like antibodies and 20 to 90 picograms per cell per day for smaller proteins in 96-well plates.

The discovery of the pMH vector series could speed drug development pipelines and reduce research costs, according to Dr. Hui. The patented expression method offers a common mechanism for accelerating all eukaryotic gene expression. The discovery of the GC-rich gene-expression method coupled with the invention of Current bioreactors "can revolutionize research and development and industrial production in the field of protein-expression technology and regulation," adds Dr. Hui.

Dual-Domain Drugs

Both technologies are being applied to a pipeline of dual-domain drugs, formed by the union of two biomolecules, with independent effects. The resulting larger molecules codistribute more efficiently into disease sites and simultaneously regulate independent disease pathways.

In theory, dual-domain drugs are ideal for treating cancer, heart disease, inflammatory conditions, and metabolic disorders. Among the dual-domain drugs in AmProtein's pipeline are ones designed to treat heart disease and cancer. Early animal studies show that dual-domain drugs are quite effective.

AmProtein has patented 20 combinations of dual-domain drugs, locking in a pipeline for the future. It is looking for partners in the U.S. and Europe to codevelop drugs in the pipeline. "We are not a company that puts our feet in just one place," Joudi comments. GEN

At-a-Glance

AmProtein

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6

Focus
AmProtein is developing a simple and efficient process for manufacturing biotherapeutics in mammalian cells using bioreactors and a GC-rich gene-expression system.