# The CHO's Over: An Inflexion Point

**Global healthcare costs and demands are changing, and the next wave of complex biologics is entering biopharma pipelines. It is time to look beyond mammalian cell lines.**

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Ever since Genentech's plasminogen activator, Activase, became the first human therapeutic product made using CHO cells in 1987, the CHO cell line has become a mainstay of the biopharma industry. Indeed, CHO cells are used to make the bestselling monoclonal antibodies (mAbs), including Rituxan, Humira and Enbrel. However, for the next wave of biologics – bi-specific and tri-specific antibodies, for example – CHO's low expression yields are driving costs beyond commercial viability for many companies. And after more than three decades of CHO cell line improvements, which have seen huge overinvestment, it seems unlikely that any incremental productivity and cost improvements will fundamentally change the game. In my view, we need to look beyond the limitations and costs of CHO – in fact beyond mammalian cell lines altogether.

Microbial cell lines may be what the industry needs in terms of production costs and speed, as well as product quality. Studies have shown that it takes around twice as long to create CHO cell lines and to prepare cells for the fermenter, when compared with microbial cell lines (1). With regard to creating mAbs, CHO entails a higher capital expenditure and operating expenditure than using microbial cell lines, and larger fermentation vessels are needed with CHO to obtain an equal output of mAbs. In addition to lower yield and longer cycle time, CHO cells require expensive enriched growth media and viral purification steps, neither of which are required with certain microbial cells. In other words, manufacturers can grow microbial cells at a lower cost for a given yield, potentially allowing next-generation biologics to be manufactured in smaller (cheaper) facilities, improving commercial viability.

Some biopharma manufacturers are beginning to recognize the limitations of CHO and are seeking alternatives; for example, Biogen's VP of International Manufacturing, Eliana Clark, said last year that they were exploring a "radical departure from the CHO platform" through research into microbial alternatives (2).

I believe one of the most promising alternatives to CHO cells, which has already proven itself in the production of biofuels and enzymes, is a genetically modified form of a fungus called Myceliophthora thermophila, nicknamed C1. C1 was developed by exposing Myceliophthora thermophila cells to ultraviolet light to induce random mutations. Scientists then expanded and reinforced potentially beneficial mutations to drastically change the shape of the cells, from long spaghetti-like strands to short, grain-sized sections. As C1 fungal cells secrete proteins from the ends of their filaments, the selection process resulted in more secreting ends, multiplying the potential total yield. The new shape also meant that C1 could be grown more easily in large tanks. According to our research, C1 offers a much shorter production time for mAbs than CHO, requires significantly smaller production facilities, and does not require viral purification (3).

I believe that C1 cells could help speed up the development, lower the production costs and improve the performance of biologic vaccines and drugs at flexible commercial scales. Eventually, C1 could even supplant CHO as the go-to expression system – at least for some companies. We believe it may also enable the development and commercialization of therapeutic products that are difficult to express at reasonable yields in CHO and other cell lines, while also being able to produce larger amounts of protein for drug discovery and development purposes.

Today, any biopharmaceutical company pondering the optimal strategy for producing a new or biosimilar biologic drug should look beyond conventional manufacturing paradigms, such as CHO. It is well worth examining how alternative methods could have beneficial results in terms of speed and cost of production, and product quality.

*References*

1. *Dyadic, "C1, An Ultra-High Yielding, Game Changing Gene Expression Platform" (2018). Available at https://bit.ly/2N3PGID. Accessed September 10, 2018.*
2. *D Stanton, "CHO stopper? Biogen looks to alternative cell lines for future of bioproduction," BioPharma Reporter (2017). Available at https://bit.ly/2O4bSit. Accessed September 10, 2018.*
3. *Dyadic, "Dyadic – C1 Technology," (2018). Available at https://bit.ly/2Qg8AKh. Accessed September 10, 2018.*