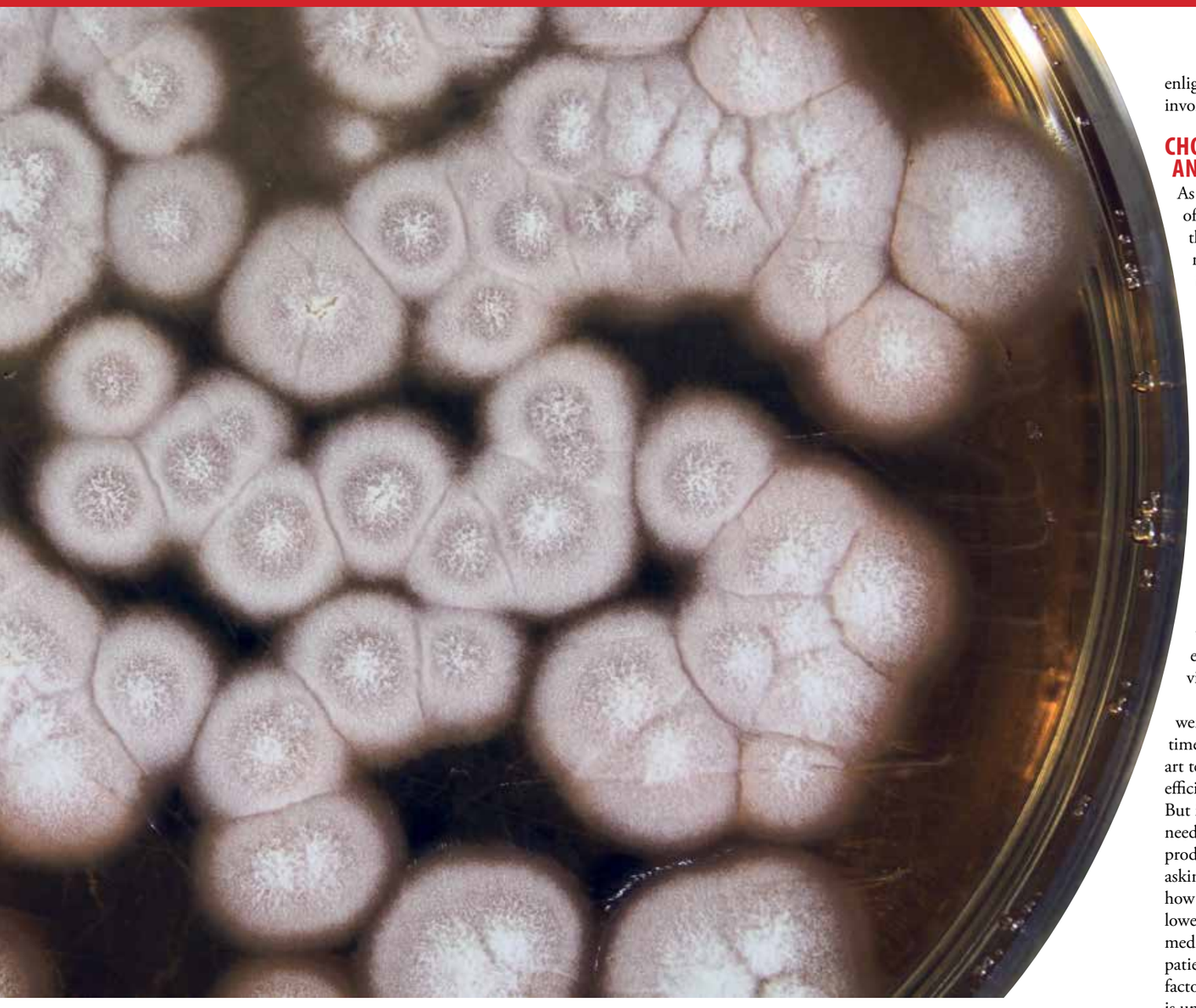


GOING BEYOND CHO

Mark Emalfarb details how to ensure efficiency in biologics production

Many pharmaceutical laboratories developing biologics such as antibodies are, for the most part, using a manufacturing technology that is rooted in the 1980s: namely, Chinese hamster ovary (CHO) cells. Yet amid growing concerns regarding the relatively high production cost and low efficiency presented by CHO, the industry is poised to embrace alternative cell lines that can operate many times faster and cheaper to speed up the development and potentially bring down the cost of the end product: medicines for human use.

Prominent among these newer cell lines is a proprietary protein expression platform based on a proprietary genetically modified strain of fungus – Myceliophthora thermophila, named C1 – that has shown promise in producing enzymes and other proteins in a shorter amount of time, in higher amounts and at a lower cost than CHO. A quick comparison of these two paradigms can be enlightening for a variety of stakeholders involved in drug development.

CHO INVOLVES DRAWBACKS AS AN INDUSTRY STANDARD

As noted in a 2017 survey, nearly half of biomanufacturing experts believe that the industry is currently too reliant on CHO. Multiple recent industry articles have delved into the various factors that are driving this sentiment. For example, data shows that it takes about twice as long to create biologic drugs using CHO cell lines compared with microbial cell lines and about twice as long to get the cells ready to go into a fermenter. With regard to the creation of monoclonal antibodies (mAbs), CHO entails a relatively higher capital expenditure and operating expenditure than the use of microbial cell lines. In addition to its relatively low yield, longer cycle time and need for large fermentation vessels, CHO also requires the use of expensive enriched growth media and viral purification steps.

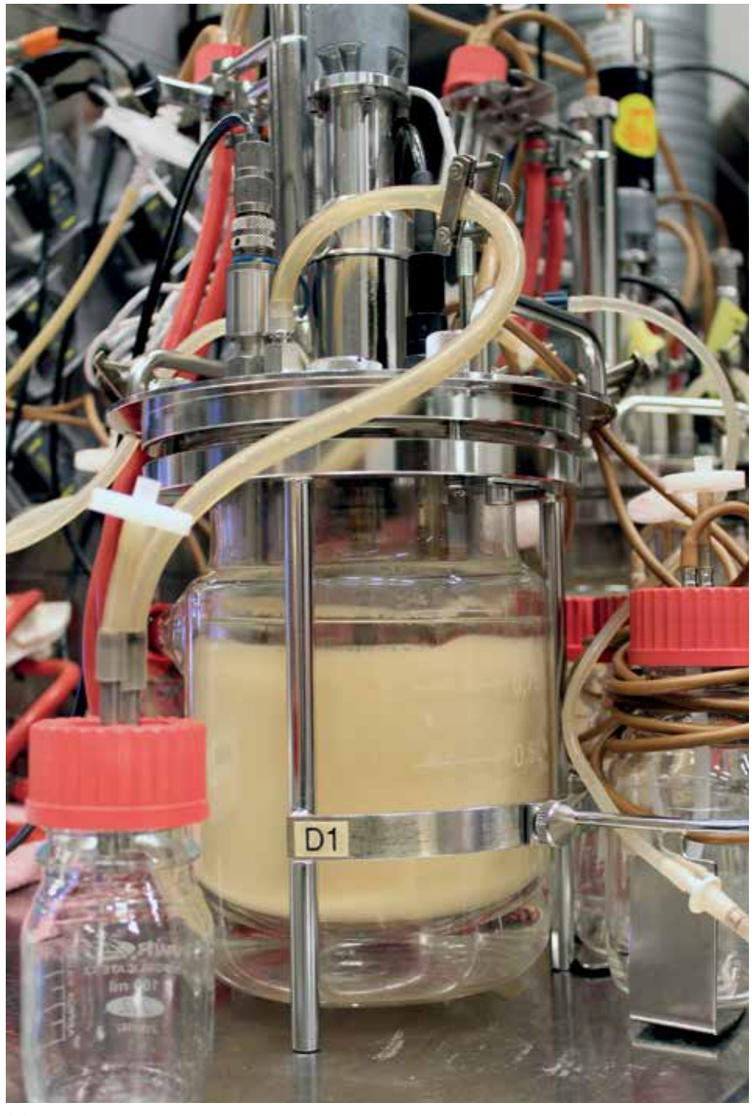
Thirty years ago, these characteristics were less of a drawback since, at that time, CHO represented the state-of-the-art technology and was the most cost-efficient option available to the industry. But in the 21st century, the growing need for greater efficiency in biologics production is reflected by those who are asking themselves an important question: how can the cost of manufacturing be lowered to a point at which these crucial medicines can be more affordable for the patients who need them? Although many factors influence the cost of drugs, there is unlikely to be much improvement on the horizon without greater production efficiency.

A NEXT-GENERATION PROTEIN EXPRESSION PLATFORM HOLDS POTENTIAL BENEFITS

In light of this need for advancement, the potential efficiency of C1 as a drug production platform is significant. The fungus' unique morphology translates into better growth conditions with higher yields of secreted protein and lower viscosity. Specifically, with up to 80% of target protein secreted, a greater amount of protein is retained via downstream processing. In addition to requiring only low-cost synthetic media, C1 is also virus-free, eliminating the need for viral inactivation and nanofiltration. Additionally, C1 accommodates wide operating conditions for pH and temperature at scales ranging from laboratory shake flasks to greater than 100,000 litre tanks and above. Importantly, C1 has been determined to be generally recognised as safe (GRAS).

These type of benefits are complemented by the shorter development and production cycle that C1 introduces. It is possible to develop gram-per-litre-per-day C1 cell lines in as little as 15 weeks. Additionally, the C1 fermentation cycle time is in the range of four to seven days, which is about one-half to one-third the time required by CHO. You can also speed up the timeline to go from seed flask to commercial fermenter, representing a savings of at least 10 to 14 days in comparison with CHO.

This translates overall into a lower production cost both in terms of capital expenditure and operating expenditure, whether a facility uses dual 12,000 litre multi-use tanks or a 2,000 litre single-use bioreactor. CapEx is reduced by C1's ability to produce drug at a smaller scale while greatly increasing protein yields;



C1 fermentor culture that resemble bacteria or yeast

meanwhile, OpEx is reduced due to the smaller facility footprint that is required along with the use of low-cost media.

NEXT STEPS IN THE DEVELOPMENT OF THE C1 PLATFORM

Given these advantages, it is natural to attempt a forecast of next steps with regard to the development of the C1 platform and its adoption and use by the pharmaceutical and biotech industries. While the efficiency of the platform continues to be refined, industry has already started to take notice. In September 2018, for example, Sanofi-Aventis entered into a fully funded proof-of-concept research collaboration to explore the potential of C1 technology to produce multiple types of biologic vaccines and drugs of interest for human health indications.

Meanwhile, Mitsubishi Tanabe Pharma is evaluating C1 technology to produce two difficult-to-express vital therapeutic proteins, also for human health, while the Israel Institute for Biological Research is evaluating C1 for the development of recombinant vaccines

Dyadic's C1 gene expression platform is based on a genetically modified strain of the fungus Myceliophthora thermophila

and neutralising agents comprising targeted antigens and monoclonal antibodies. The ZAPI vaccination programme, a branch of the Zoonoses Anticipation and Preparedness Initiative, a large-scale public-private partnership between the European Union and the pharmaceutical industry association EFPIA, found that a C1-expressed antigen tested in a small mice study generated the desired immune response and no negative health effects.

The overarching goal of these and other activities is to demonstrate the key role that C1 could play in enhancing the efficiency of the development of biologics, enabling the development and commercialisation of genes that are difficult to express at reasonable yields in CHO, and even evaluating C1's potential role in drug discovery and development.

The pharmaceutical and biotech industries would do well to continue investigating the shortcomings of the current CHO-based paradigm as well as the advantages presented by viable alternatives. By clarifying CHO's limitations and studying the potential advances represented by C1, a future marked by greater production efficiency and greater access to needed medicines among the patient population could result. ●

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A LOOK AT THE C1 TECHNOLOGY

Over the past two decades Dyadic has developed an industrially proven expression system based on the fungus Myceliophthora thermophila, nicknamed C1. The C1 technology is a robust and versatile fungal expression system for gene discovery, development and production of enzymes and other proteins. It is an optimised and industrially proven system that turns genes into a broad range of valuable products. The C1 technology platform helps to overcome some of the inadequacies of existing expression technologies used for gene discovery, product development and commercialisation. It is one of a very few commercially available solutions able to efficiently uptake genes and develop highly scalable industrial processes to produce large volumes of affordable enzymes and other protein products. This fully programmable system is robust, flexible and safe and has produced products in some of the largest fermenters used in the biotechnology industry.

Based on the firm's academic and commercial collaborations, it believes that experts in academia and industry regard the expression system as among the foremost expression systems in the world. The company has successfully licensed its C1 expression system, on a non-exclusive basis, to some of the world's largest and most renowned industrial biotechnology companies such as Abengoa, BASF and Codexis, among others.

The company is optimistic about the impact that the C1 expression system may have on the development and manufacturing of biologic vaccines and drugs and that using the system may be the critical differentiator in allowing Dyadic, its collaborators and licensees to compete in these technology-driven markets.

Further, it believes that biologics developed without the most productive expression system will face reimbursement challenges. ●