

AUTOMATED AND ENHANCED CLONE SCREENING USING A FULLY AUTOMATED MICROTITER PLATE-BASED SYSTEM FOR SUSPENSION CELL CULTURE

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In this talk we will present how we accelerated a clone selection process by 4 weeks while increasing the information density obtained for each clone. This was achieved by increasing the throughput and integrating new powerful analytical technologies as gene expressions and glycosylation analysis at a very early stage. Additionally, we could identify the overall top clone that was lost during the pre-selection phase of the reference process which is based on a considerably lower automation degree.

Using our in-house developed MTP-based cell culture system for clone screening and selection offers substantial potential for improvement and acceleration: The system provides a fully automated process and enables fed-batch cultivation at an early stage which is of high importance for successful clone selection. Due the high throughput of more than 600 cultivations at the same time the MTP-based system considerably increases the number of clones that can be evaluated and speeds up the processing. The potential to integrate real-time monitoring of metabolites and other secondary selection criteria crucial for productivity and product quality further supports reliable clone selection. Moreover, the MTP-based system establishes an interface for advanced HT analytics to identify additional parameters for clone evaluation. Thus, we demonstrated the technical feasibility to couple the MTP-based cell culture system with glycosylation analysis as well as the LightCycler® technology to perform automated RT-qPCR gene expression analysis for a large number of cell culture samples. The results of the RT-qPCR analysis showed that the identified top clone displayed the highest mRNA expression level for the HC of the examined mAb which correlated with the highest specific productivity recorded at the protein level. Furthermore, RT-qPCR analysis may also be beneficial to monitor the expression of stress markers like chaperones and factors related to endoplasmic reticulum stress potentially correlating with product concentration or it can be applied to improve prediction of clone stability attributes related to promoter methylation or transgene copy number.

This particular advancement combined with the high flexibility of the system opens up future perspectives for optimizing the selection process at an early stage, e.g. by using multiple selection criteria that are especially tailored for each product. The early availability of product quality data will also improve the chances to select the most suitable clone and to reduce risks and required effort during later development stages. This is of particular importance when expressing complex molecule formats such as bispecific antibodies, glycoengineered antibodies or antibody cytokine fusion proteins. Our high-throughput MTP-based cell culture system appears most suitable to enhance efficiency and robustness of the clone screening procedure as well as the quality of the selected clones. Product quality control can be reached by selecting the clone with the desired product quality pattern at a very early stage using our cell culture system that is proven to be predictive for large scale bioreactors.