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Short Commentary on Optimization of a Transient Antibody Expression Platform Towards High Titer and Efficiency

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Description

A Transient Gene Expression(TGE) workflow with high throughput capabilities is the hallmark of an early discovery platform in the realm of Biologics. Meeting the protein demands for early research and discovery (varying in the range from few mg to larger gram quantities for pre-clinical *in-vivo* POC studies) is perfectly suited and delivered by a TGE platform. Additionally, TGE platform has significant promise for gene therapy applications including production of innovative viral vectors and virus-like particles.

The publication describes the establishment and optimization of such a platform (developed mainly for mAbs) with unique innovations including reduction in quantity of coding DNA as well as elucidating the kinetics of the transfection complex formation[1]. This paper, for the first time, used the concept of Filler DNA (substituting the coding DNA) for early discovery research, and application of the same across multiple molecule modalities (e.g., regular mAbs, bi-, and multi-specifics). Additionally, the authors have focused on the transfection phenomenon and have illustrated the intermix of various parameters which governs the performance of the process. With transient gene expression, a multitude of inter-dependent factors contribute towards the final outcome of the product. Three broader categories including, i) DNA and vector elements (vector design, promotor, codon usage, signal peptide, genetic elements); ii) Transfection process (amount of DNA, Transfection Reagent (TR), ratio of DNA:TR, kinetics of complex formation, cell density at transfection); and iii) Cells and culture conditions (including feeding strategy, temperature shift), are the major strings in the orchestra of TGE. The current paper zooms into the 'transfection process' and elucidates the intricacies of different factors that influences the final titer in mAb production. The authors have described a process which is robust, efficient, cost-effective and is amenable to high throughput.

In the paper, the authors shed light upon the kinetics of the TR:DNA complex formation *via* DLS[2]. They demonstrated that the complex formation is an instantaneous phenomenon which unfolds as soon as the DNA and TR are together in the serum free complexation medium. The optimal size of this complex (which is taken up by the cells) is generated at the very onset of the process when the DNA and TR come together. Though there is a slight increase in the complex size (hydrodynamic radius) over time; this does not have any direct correlation with the final titer. The authors have demonstrated that the ideal sized complex is initiated and formed at the onset which is ideal for the cellular uptake by the suspension CHO cells. This is a unique finding for a TGE process and has direct benefits of reducing the sample handling time, especially when dealing with hundreds of samples in parallel in early stages of discovery.

Another significant finding in the field of transient transfection/TGE as elucidated by the authors is the substitution of the coding DNA by Filler DNA. It has been clearly demonstrated in the manuscript that substituting 70% of the coding DNA with Filler DNA has no impact in the titer, product quality and functional output of the molecules. The authors have done a thorough characterization of molecules produced using Filler DNA across multiple formats and have observed no difference. Implementation of this advancement leads to significant cost savings in the TGE process. Data from the DLS also elucidated that inclusion of the Filler DNA did not result in any change in the size of the transfection complex; and that the optimal sized complex that is taken up by the cells is formed at the onset of the process.In summary, the authors evaluated empirically a matrix of factors that impacts the TGE process and have generated an optimal protocol which generally produces high titers and sufficient material for early discovery studies and pre-clinical evaluation. This paper clearly demonstrated several process improvements in a CHO-E based transient expression platform with better yields and product quality.

References

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