

New Cell Engineering Method for Increasing Recombinant Therapeutic Antibody Productivity Up To 10-Fold in Batch CHO Cultures

Kathy Ngo¹, Lawrence Chasin², Larry Forman¹

¹CHO Plus, Inc., South San Francisco, CA, ²Columbia University, New York, NY



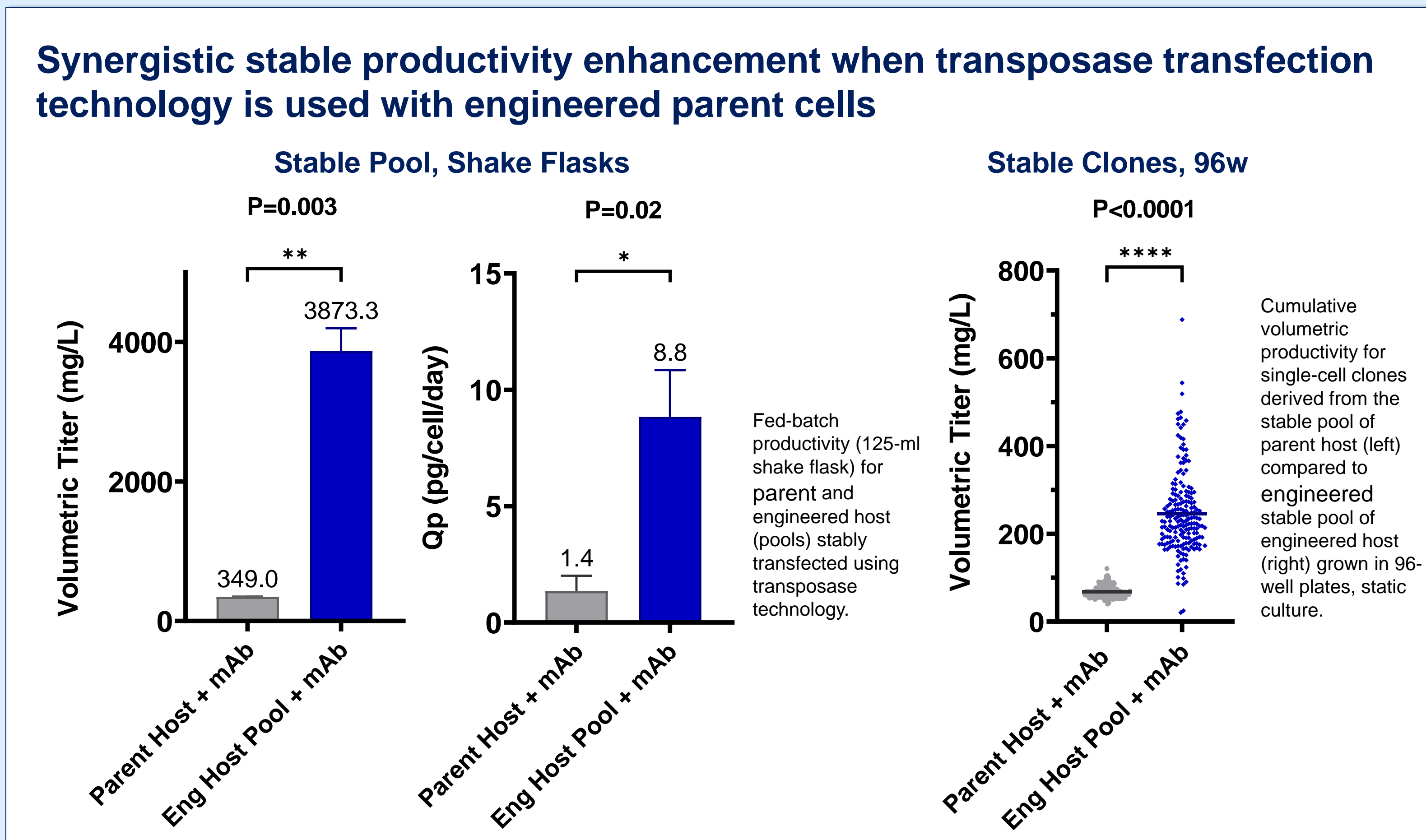
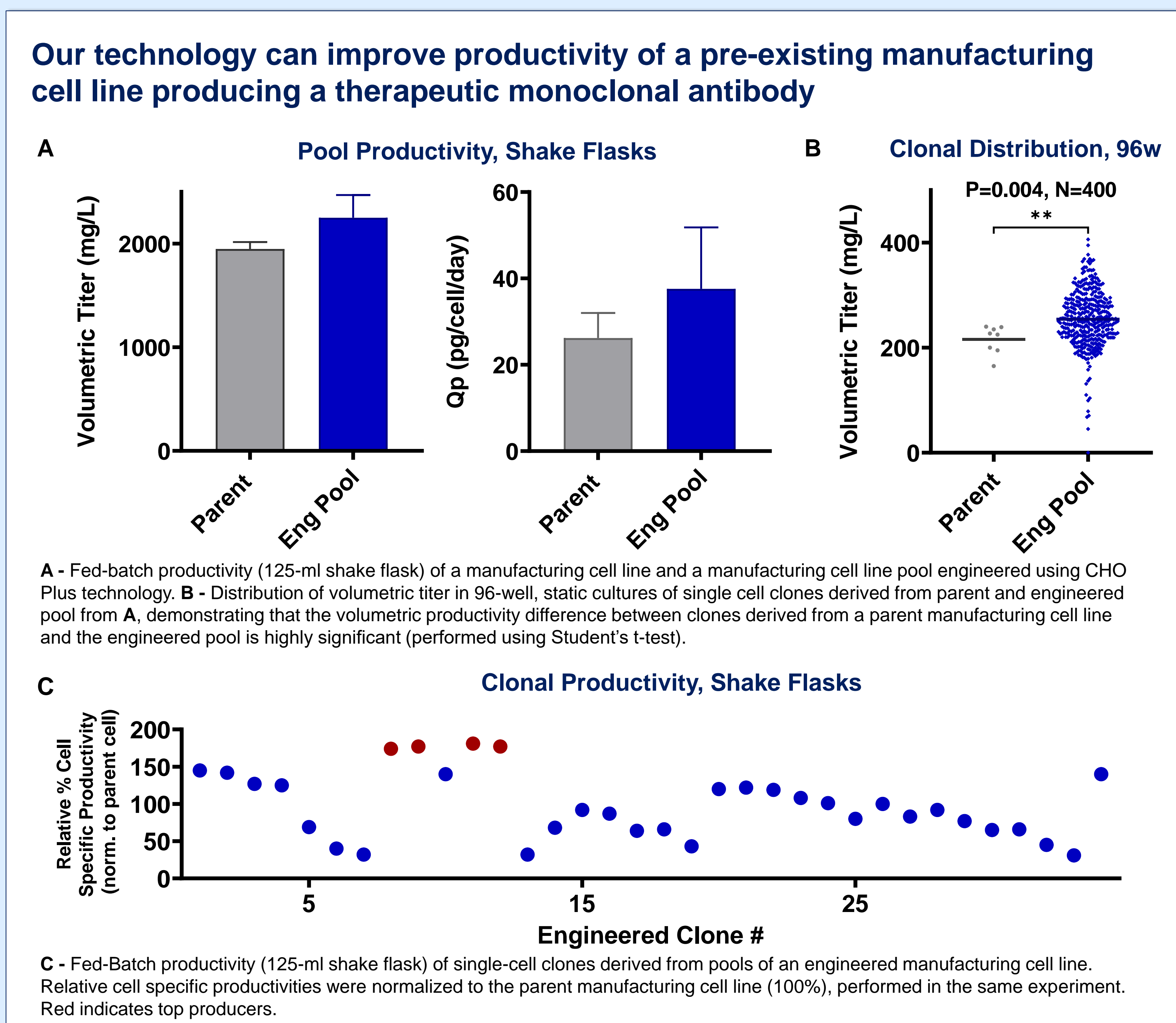
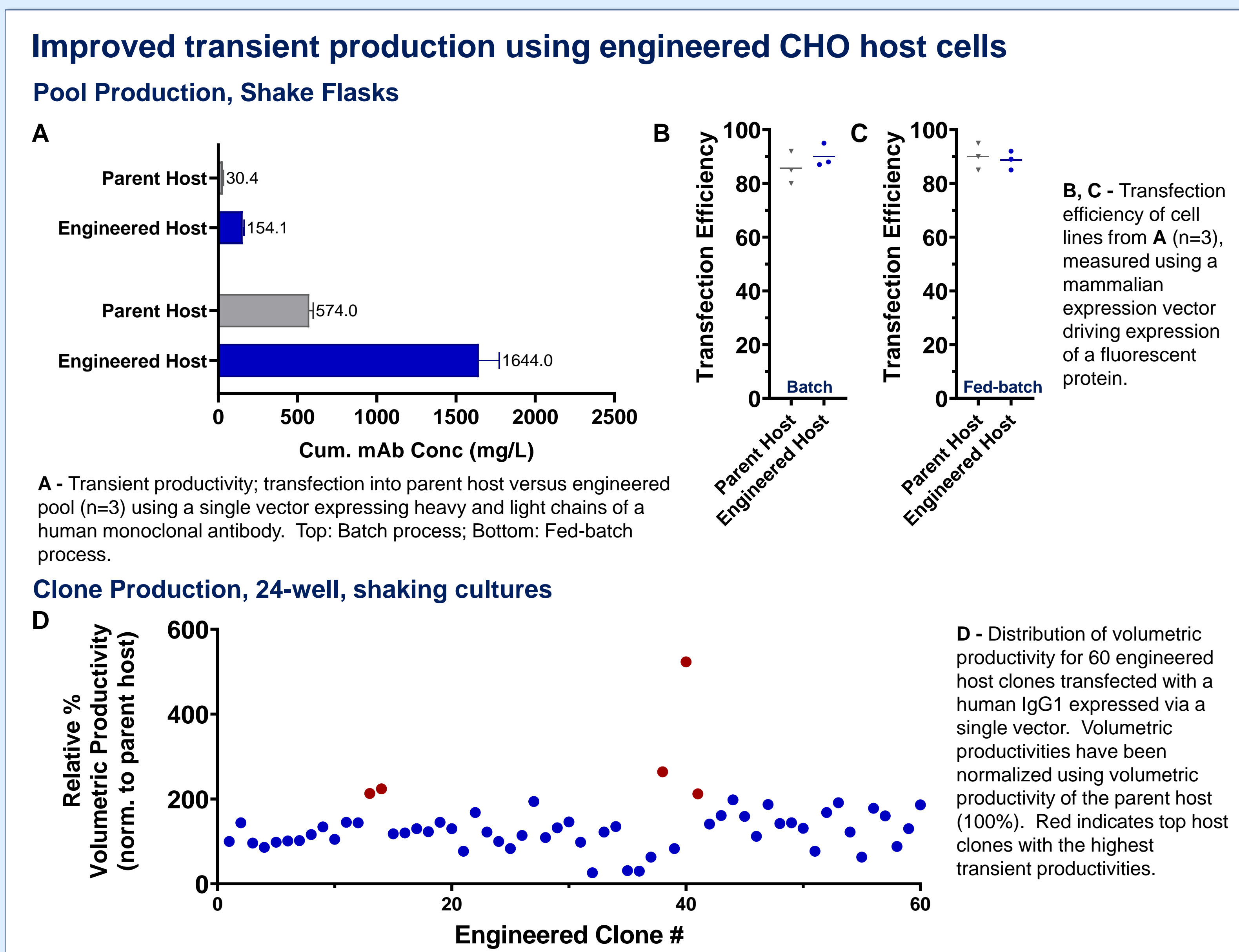
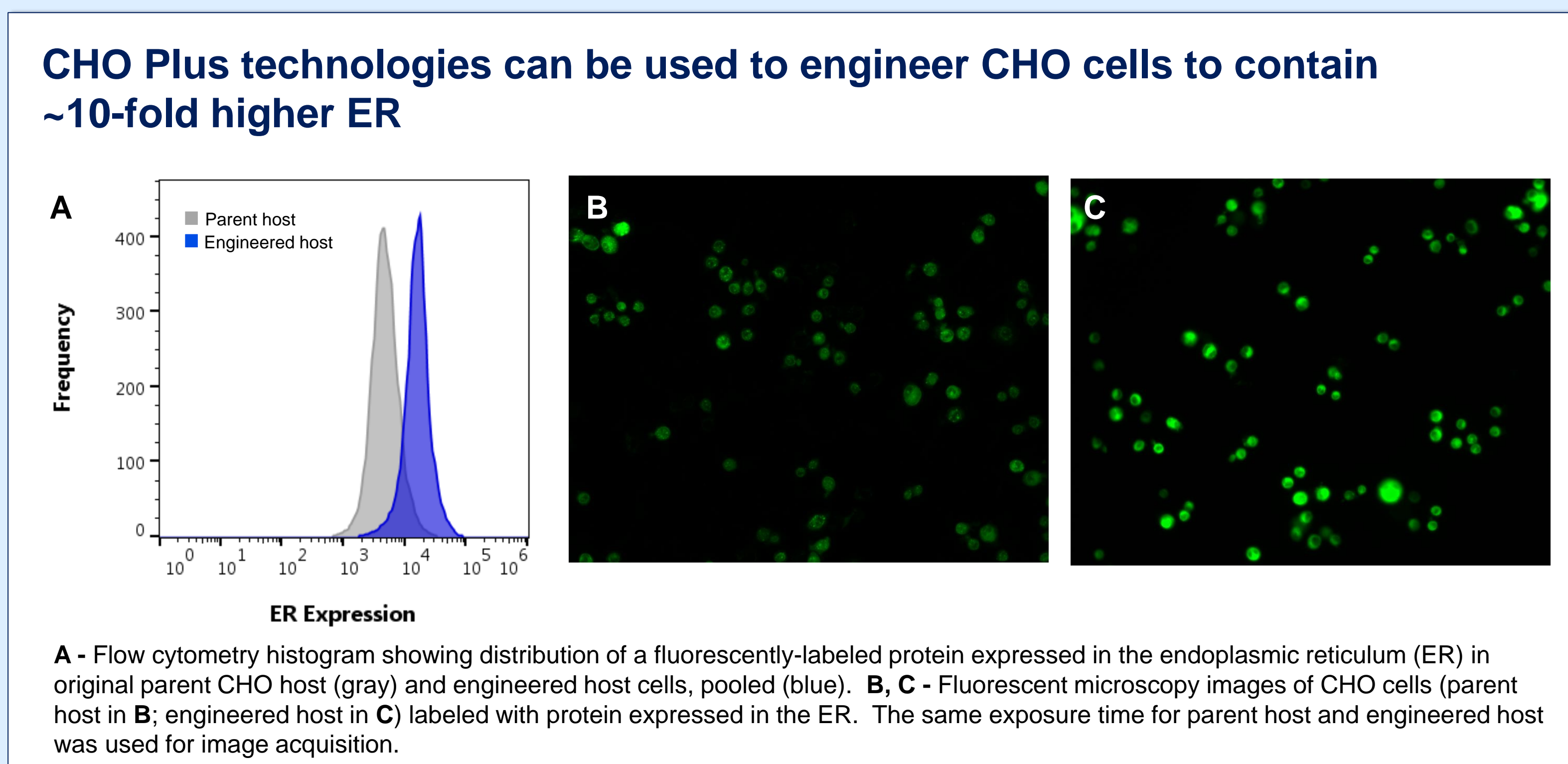
ABSTRACT

Background and Novelty: Despite decades of cell culture process improvements and cell engineering methods development, there remain intrinsic bottlenecks to higher recombinant protein productivity using Chinese hamster ovary (CHO) cells. These bottlenecks limit CHO cell-based manufacturing potential. Here we disclose a directed evolution strategy to genetically engineer and select for CHO cells with enhanced protein-production machinery. Our innovative approach circumvents natural limitations present in CHO cells, positioning it to become a new and vastly improved manufacturing paradigm for recombinant therapeutic protein production.

Experimental approach: Homotypic fusions of CHO cells were selected for high expression of proteins associated with endoplasmic reticulum (ER). Fused cell hybrids advantageously selected for enhanced ER (up to >10-fold higher ER) were evaluated for recombinant protein production by transient and stable transfection of a recombinant human therapeutic monoclonal antibody (mAb).

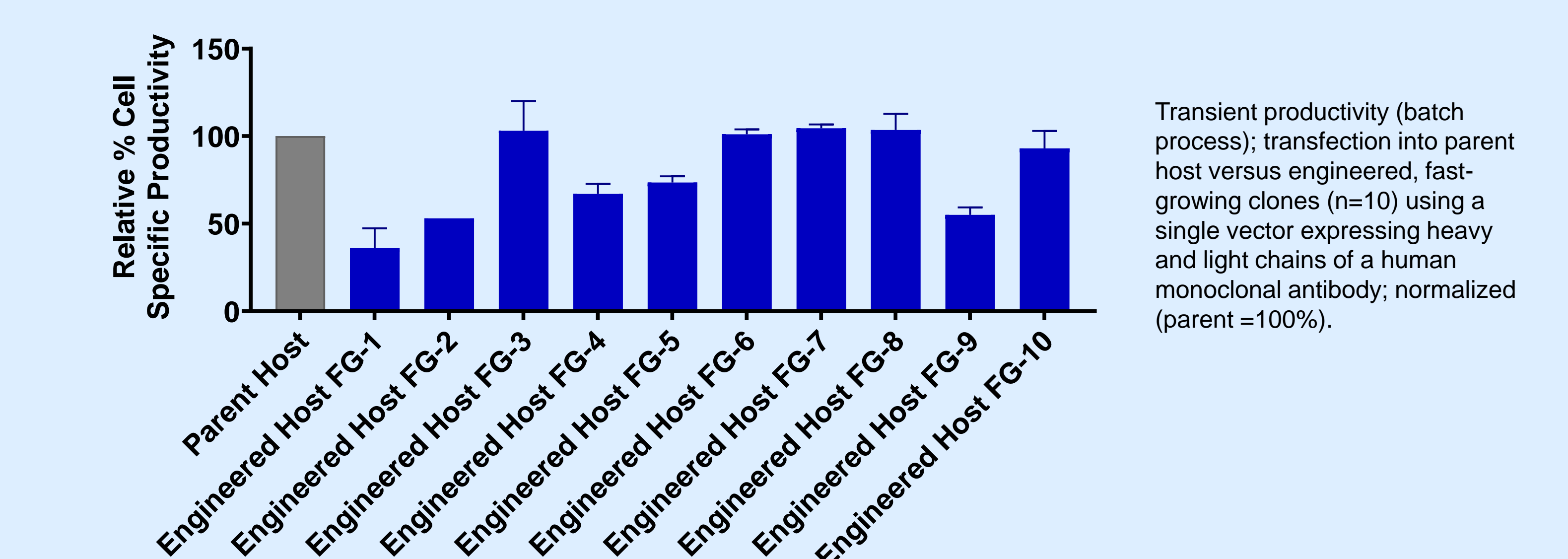
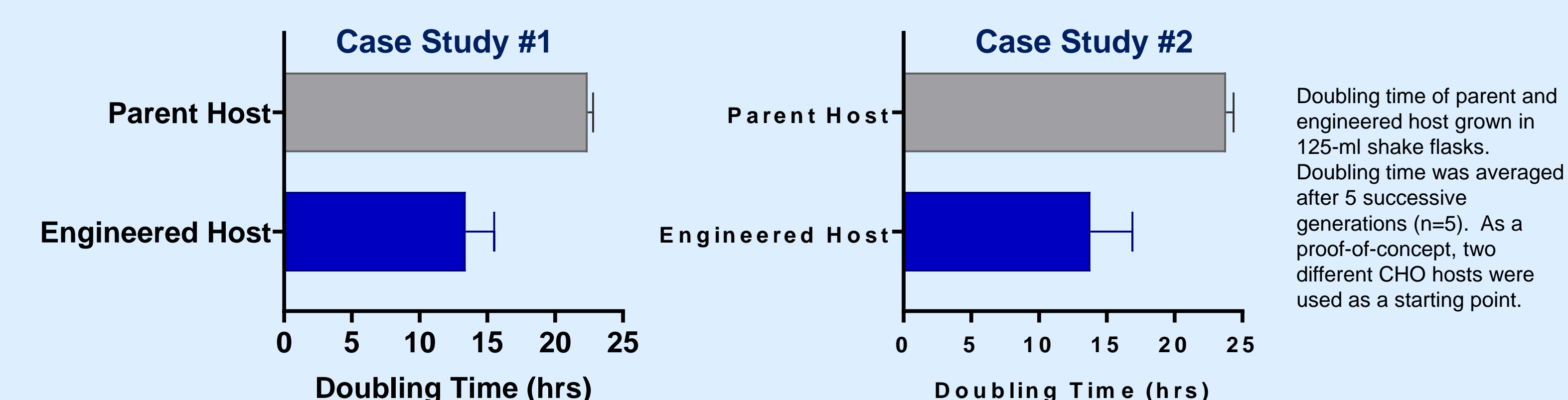
Results and discussion: CHO cells engineered using our approach exhibited enhanced transient cell specific and volumetric productivities for a human mAb of up to 4-fold compared to un-engineered parental cells in batch cultures. For stable transfection, up to 10-fold increases were observed for specific and volumetric productivities for engineered cells expressing recombinant human mAbs at the transfected-pool stage.

We have demonstrated that our cell engineering technologies, leveraging directed evolution methods, represent a novel and disruptive platform for vastly improving CHO cell manufacturing capabilities.



DISCUSSION

CHO Plus platform can be used to engineer-in additional advantageous phenotypes, such as faster growth, while maintaining productivity:



CONCLUSION

We demonstrate a disruptive platform to enhance CHO manufacturing capabilities:

- + Synergistic productivity enhancement in engineered cells when used with transposase technology
- + Cell growth rate increased by 50% while maintaining initial cell-specific productivity
- + Up to 10-fold increase in productivity via transient and stable transfections
- + Up to 4 g/L cumulative volumetric productivity demonstrated for stably-transfected pools
- + Additional phenotypes, such as faster growth—and others, can be engineered into host cells