PROGRESS TOWARDS MAKING A GLOBAL SUPPLY OF MICROBIAL EXTRACELLULAR VESICLES, 100-TIMES CHEAPER THAN A TYPICAL BIOLOGIC

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Evelo Biosciences is pioneering a new therapeutic modality, based on microbial-derived extracellular vesicles (EVs). This platform provides biological efficacy and safety, at a cost point that aims to enable access of biologics on a global scale. This promise comes significant challenges in meeting the demand, while achieving the COGM targets. As the envisioned demand reaches far beyond what can be provided even at 20,000-L batch-scale, we are driving toward the implementation of ICB and accompanying technologies, such as 20,000-scale perfusion, continuous downstream and formulation.

Extracellular vesicles are a complex drug product, derived as naturally occurring lipoprotein nanoparticles and delivered as an oral solid dosage form (pills). They are ~100nm lipid by-layer vesicles containing substantial quantities of proteins, glycans, and LPS, imbedded in the membrane. As an added challenge, our EVs are derived from obligate anaerobes, making the production and scaling of the fermentations complex.

The primary limitation to fermentation of obligate anaerobes is a buildup of inhibitory metabolites, due to poor substrate utilization. We have developed a tangential flow filtration (TFF) perfusion process that simultaneously collects the EVs, as a cell-free permeate stream, and reduces the waste products in the culture. Sustained high recovery of product in the permeate stream was achieved through screening of TFF filters, fluxes, and flow rates. Regarding product capture, the limitations of conventional bead-based liquid chromatography were overcome by using a large channel monolith columns, wherein binding efficiency is negligibly impacted by flow rate, and binding of a 50 – 200 nm product is not limited by pore size.

We will describe a conceptual integrated continuous bioprocess for the very large-scale production of EVs and provide proof-of-feasibility data for key technologies, demonstrating the capability to dramatically improve batch productivity (>30-fold increase in daily output). Our results support the potential for large-scale production of EVs for the commercial market. We consider these results a strong step towards achieving Evelo's stated goal to provide safe medicines to billions of patients around the globe.