DEVELOPMENT OF A LARGE SCALE GMP COMPLIANT SUSPENSION CELL CULTURE SYSTEM FOR THE MANUFACTURING OF ALLOGENIC EXOSOME-BASED BIOTHERAPEUTICS

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Key Words: exosomes, extracellular vesicles, chemically-defined media, suspension culture, GMP.

As efforts accelerate to translate exosome biology into new medicines, clear technology gaps have emerged between the current state of the art for producing extracellular vesicles (EVs), comprising exosomes, and the capabilities necessary to support large scale clinical and commercial manufacturing. An allogenic EV production system is necessary to make the technology viable for a broad range of therapies and large patient populations. To this end, Codiak BioSciences has leveraged cutting edge bioprocessing methods developed through decades of recombinant protein manufacturing to create a >1,000-fold scalable exosome production platform based on an immortalized human cell line growing in suspension and chemically defined media.
Until recently, EVs have been produced largely in discovery labs where process scale up and manufacturability were not of prime concern for this novel biotherapeutic modality. Using an established human cell line, we first developed a lab scale production process, which we then scaled up to bench scale and pilot scale through optimization of key process parameters, such as pH, gassing, and agitation. To expediently produce clinical material for our first program, we implemented a fed-batch process. However, with the goal for this platform to support a portfolio of clinical programs in the future, parallel efforts were focused on the development of a second generation production process using continuous technology. Importantly, our studies revealed a direct, positive correlation between bioreactor cell mass and EV productivity. Moreover, improvement in culture health was as important as the increase in biomass, since higher culture viabilities minimized contamination of the harvest with microvesicular and other membranous impurities, proteinaceous material, nucleic acids, and other small molecules—a positive outcome for downstream processing. Our results indicate that EVs can be efficiently produced in stirred-tank bioreactors in a fed-batch and continuous process representative of large scale manufacturing under GMP conditions. Due to process comparability at different platforms, the intermediate scales can be used to provide uniform batches of development material for discovery research. The EVs produced are strongly positive for canonical exosome markers such as tetraspanins, have classical exosome morphology by TEM, and are capable of fusing with recipient cells, although the effect of process manipulations on EV quality has not yet been fully understood. Lastly, our current process is robust, relies on standard bioprocessing infrastructure found at most CMOs and is compatible with single use disposable technology.