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Large-Scale Production and Therapeutic Evaluation of Exosomes for Cancer Treatment

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INTRODUCTION: Lung cancer remains one of the most prevalent and deadly malignancies worldwide, representing a major global health challenge. According to the latest global cancer statistics, lung cancer accounts for approximately 11.6% of all new cancer diagnoses and 19.8% of cancer-related deaths, making it the leading cause of cancer mortality.[1] Current therapeutic strategies, including surgery, chemotherapy, radiotherapy, and targeted therapies, vary depending on the histological type and stage of the tumor. While these approaches have improved survival in select patient populations, their overall effectiveness remains unsatisfactory due to systemic toxicity, drug resistance, and tumor recurrence. Consequently, there is an urgent need to develop safer, more effective, and targeted therapeutic strategies capable of overcoming these limitations.[2]

Recent advances in immunotherapy and nanotechnology have transformed the landscape of cancer treatment, enabling precise modulation of tumor immunity and site-specific delivery of therapeutic agents. Among the various nanocarrier systems, such as liposomes, polymeric nanoparticles, developed to date, exosomes have attracted attention as a promising next-generation therapeutic tool for cancer diagnosis, treatment, and prognosis.[3] Exosomes are naturally derived, cell-secreted nanovesicles with intrinsic biological functions. Exosomes are lipid bilayer vesicles with diameters typically ranging between 30 and 150 nm, secreted by most eukaryotic and prokaryotic cells under both physiological and pathological conditions. They are formed through the endosomal pathway and encapsulate a rich cargo of proteins, lipids, nucleic acids, and metabolites reflective of their cell of origin. Due to their endogenous origin, exosomes exhibit exceptional biocompatibility, low immunogenicity, and the ability to cross biological barriers such as the blood–brain barrier, features that confer them a distinct advantage over synthetic nanoparticles. Furthermore, their inherent role in intercellular communication allows them to mediate the transfer of bioactive molecules between cells, influencing diverse biological processes including immune regulation, angiogenesis, and metastasis.[4,5] These properties position exosomes as promising candidates for both diagnostic and therapeutic applications in cancer.

In recent years, the use of exosomes as liquid biopsy biomarkers for early detection of cancer has gained attention. Because exosomes can be readily isolated from non-invasive sources such as plasma, serum, or bronchoalveolar lavage fluid, they provide valuable molecular insights into tumor progression and response to therapy.[6] Beyond diagnostics, exosomes also offer unique advantages as therapeutic delivery vehicles. Their natural targeting capabilities, long circulation time, and ability to encapsulate and protect therapeutic molecules such as small RNAs, proteins, or antigens make them ideal candidates for precision drug delivery. Specifically, in oncology, exosome-based delivery systems can enhance drug accumulation within tumor tissues, minimize systemic toxicity, and improve overall therapeutic efficacy compared with conventional chemotherapeutics. Despite these advantages,

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one of the major challenges impeding the clinical translation of exosome-based therapeutics is the difficulty of large-scale production and purification. Exosomes are typically secreted at low concentrations, and traditional isolation methods such as ultracentrifugation, precipitation, or size-exclusion chromatography are often labor-intensive, time-consuming, and yield-limited. Therefore, optimizing scalable, reproducible and cost-effective bioprocesses for the large-scale production and purification of exosomes is a critical prerequisite for their preclinical and clinical application.[4,5] Addressing these limitations will be a crucial step toward realizing the full potential of exosome-based nanomedicine as a next-generation therapeutic strategy in the treatment of lung cancer and other malignancies.

MATERIAL AND METHODS: In the present study, THP-1 cells, a well-established human pro-monocytic cell line, were selected for exosome production due to their immune-regulatory potential and capacity to secrete vesicles rich in functional proteins and cytokines. To ensure the isolation of exosomes exclusively secreted by THP-1 cells, the culture system was adapted to serum-free conditions, eliminating contamination from animal-derived exosomes commonly present in fetal bovine serum.[7] Subsequently, cells were produced in a stirred-tank bioreactor, and a cross-flow ultrafiltration system was optimized for isolation, creating a bioprocess system for large-scale production of exosomes. The isolated exosomes were characterized for size distribution, morphology, homogeneity, concentration, protein content, and surface markers. Finally, after loading the cargo molecule into exosomes, their therapeutic efficacy was further evaluated in a three-dimensional carcinoma spheroid model (Figure 1).

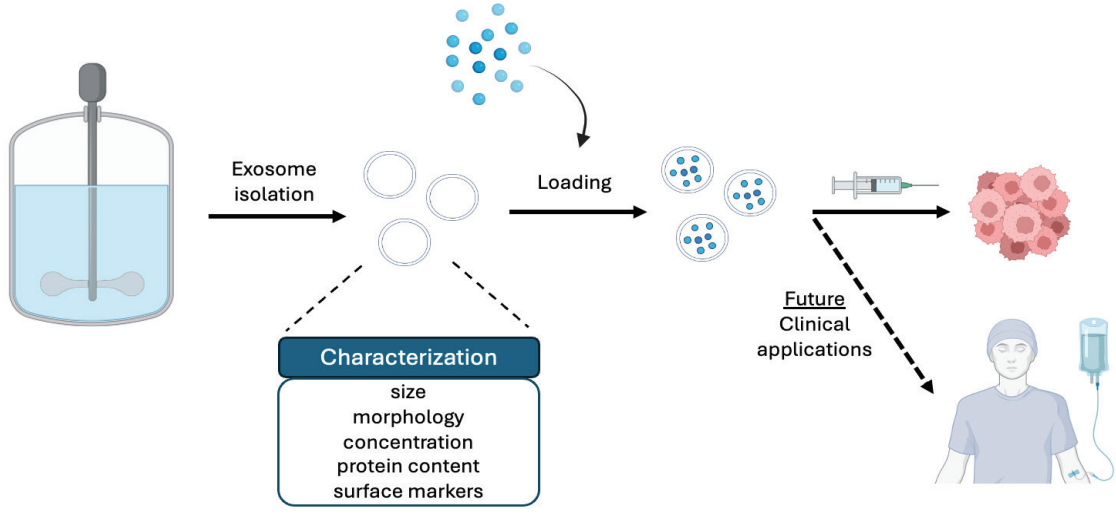

Figure 1. Schematic representation of the large-scale production, isolation, and therapeutic evaluation of THP-1-derived exosomes

RESULTS: THP-1 cells successfully adapted to serum-free culture conditions and produced exosomes efficiently in a stirred-tank bioreactor. The optimized ultrafiltration system achieved high recovery rates and excellent exosome purity, as validated by nanoparticle tracking analysis, scanning transmission electron microscopy, and immunoblotting for characteristic exosomal markers. The improved bioprocess significantly increased exosome yield, thereby overcoming one of the major bottlenecks in their clinical scalability. Functionally, the application of loaded THP-1-derived exosomes to carcinoma spheroids led to a notable reduction in spheroid size and cell viability, demonstrating their potential tumor-suppressive and antigen-delivery capabilities. These findings highlight the immunostimulatory potential of immune cell-derived exosomes, which may act through pathways involving antigen presentation and modulation of immune signaling cascades. The scalability of this bioprocess,

combined with the therapeutic efficacy of THP-1-derived exosomes, emphasize their promise as next-generation immunotherapeutic platforms for cancer treatment.

CONCLUSION: This study comprises a progress about a scalable bioprocess platform for the efficient production, purification, and functional validation of THP-1-derived exosomes. The optimized stirred-tank bioreactor and cross-flow ultrafiltration system significantly improved exosome yield and purity, enabling the quantities required for preclinical applications. Functionally, the resulting exosomes demonstrated potent antitumor effects in 3D tumor models, supporting their potential use as immunomodulatory nanotherapeutics in oncology. Future research should focus on optimizing cargo loading strategies, *in vivo* biodistribution analysis, and optimization of targeting strategies for specific tumor types, including lung cancer. Ultimately, integrating scalable manufacturing with precise therapeutic design will accelerate the clinical translation of immune cell-derived exosomes as safe and effective platforms in cancer nanomedicine.

KEYWORDS: Exosomes, cancer, large-scale production, THP-1 cells, nanotechnology in oncology

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