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Minireview

Advanced Culture Media as a Cornerstone for the Clinical Translation of Exosome Therapeutics

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ABSTRACT

The transition from serum-based culture systems to chemically defined media (CDM) represents a pivotal advancement in the development of therapeutic extracellular vesicles (EVs). Traditional use of fetal bovine serum (FBS) introduces substantial variability and risk of contamination, hampering both clinical translation and mechanistic clarity in EV research. While serum-free (SFM), xeno-free (XF), and animal component-free (ACF) formulations offer incremental improvements, only CDM ensures maximal reproducibility, safety, and the capacity for biomanufacturing at scale. Nonetheless, developing one-size-fits-all CDM remains inherently challenging due to the complex, cell-type-specific metabolic requirements and the unmatched molecular richness of serum. Recent progress has been particularly notable in CDM optimized for mesenchymal stem cells and epithelial cells, enabling both higher EV yield and manipulation of EV cargo toward enhanced therapeutic function. Advances in high-throughput screening (HTS), design of experiments (DoE), and artificial intelligence (AI) now enable systematic optimization of multi-component media formulations, marking a paradigm shift from passive support to active regulation of EV composition and bioactivity. CDM is no longer merely a cleaner alternative but a precision-engineering platform central to the production of next-generation EV therapeutics. As biomanufacturing converges with computational design and automation, the ability to tailor EV content through media engineering may redefine standards in regenerative medicine and cell-free therapy.

BACKGROUND

Exosomes, once regarded merely as cellular waste products, have now emerged as essential mediators of intercellular communication in both physiological and pathological conditions [1]. These extracellular vesicles (EVs), typically 30–150 nm in diameter, are secreted by nearly all cell types and participate in a wide range of biological processes, from maintaining cellular homeostasis to driving disease progression [2]. One of the most distinctive features of exosomes lies in the complexity of their cargo—an intricate mixture of proteins, lipids, metabolites, and nucleic acids, including mRNA, miRNA, and DNA [3]. This cargo reflects the physiological and pathological state of the parent cell, making exosomes highly valuable as diagnostic biomarkers for various diseases, including cancer, cardiovascular disorders, and neurodegenerative conditions [4]. For example, tumor-derived exosomes, which carry cancer-specific molecules, are increasingly recognized as promising tools for liquid biopsy, enabling early detection and disease monitoring [5].

Therapeutically, exosomes offer several advantages over con-

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ventional treatment approaches, such as biocompatibility, low immunogenicity, and the ability to cross biological barriers like the blood–brain barrier [1]. Some exosomes, particularly those derived from mesenchymal stem cells (MSCs), exhibit inherent therapeutic effects by promoting tissue regeneration and modulating inflammation [6,7]. Furthermore, exosomes can be engineered as sophisticated delivery vehicles by loading them with therapeutic agents (e.g., siRNAs, miRNAs) or functionalizing their surfaces, enabling precise targeting of specific cells or tissues [8]. At the foundation of both diagnostic and therapeutic applications is the efficient isolation of pure and intact exosomes from various biological sources, including cell culture media [1]. The ability to obtain uncontaminated exosome samples is a critical prerequisite for developing exosome-based diagnostics and therapeutics [5].

A fundamental challenge in exosome research is contamination during isolation, particularly from FBS, a commonly used cell culture supplement [9]. Although FBS supports cell growth through its rich but undefined mixture of nutrients, it introduces contaminants such as bovine-derived EVs and abundant bovine microRNAs (miRNAs), both of which are nearly indistinguishable from human-derived exosomes and RNAs [10]. Consequently, isolated exosome samples often contain mixed populations, complicating the interpretation of their biological effects and transcriptomic profiles [11,12]. Additionally, FBS-derived protein aggregates and lipoproteins, which resemble exosomes in size and density, further compromise purity and accuracy in exosome quantification [13]. The presence of such contaminants is widely recognized as a critical barrier to the clinical translation of exosome research and underscores the need for standardized protocols in exosome culture and purification [9].

In fact, the widespread use of FBS during the early days of exosome research may have contributed to substantial confounding, calling for a reassessment of foundational findings using serum-free or chemically defined culture systems. Early studies mainly focused on proving the existence and fundamental function of exosomes, almost universally relying on FBS-containing culture media. The recognition of FBS-derived EV contamination came later. Thus, many initial biological findings may have been driven by a combination of human and bovine-derived vesicles or other undefined factors in FBS. These issues highlight the importance of rigorous experimental controls and suggest that key early discoveries in the field should be reevaluated under refined and defined conditions.

MAIN CONTENT

Temporary Measures and Their Inherent Limitations

To address the problem of FBS-derived contaminants in exosome research, several interim solutions have been proposed. These approaches primarily focus on the physical removal of bovine EVs from FBS; however, they are inherently limited and fall short of providing a definitive resolution.

Ultracentrifugation for Depleting Serum-Derived Exosomes: A Double-Edged Sword

Ultracentrifugation (UC) has long been considered the gold standard for both isolating exosomes and depleting serum-derived vesicles [14]. The principle of UC involves separating particles based on size and density using high-speed centrifugal force. To deplete exosomes, FBS is commonly subjected to extended ultracentrifugation (e.g., 120,000 × g for 18 hours), and the resulting supernatant is used as exosome-depleted serum. However, this method presents several critical drawbacks.

First, the removal is inefficient and incomplete. Even after prolonged centrifugation, a substantial number of vesicles and other nanoparticles remain in the supernatant [9]. While some reduction in RNA content is observed, complete elimination is rarely achieved, making the term depleted misleading. Second, essential components are co-precipitated. The intense centrifugal force is non-selective, causing not only vesicles but also crucial bioactive molecules—such as growth factors and proteins—to sediment [15]. This creates a nutrient-deprived culture medium that may impose stress on cells and alter both their intrinsic biology and the properties of the exosomes they secrete [16]. Third, vesicle integrity may be compromised. Repeated or prolonged UC can damage the structural and biological integrity of residual vesicles and promote aggregation, thereby complicating downstream analyses [17]. Fourth, the process is labor-intensive and poorly standardized. It requires considerable time, specialized equipment, and is highly sensitive to variables such as rotor type, temperature, and sample viscosity, all of which hinder reproducibility between laboratories [14]. Alternative physical methods—such as tangential flow filtration (TFF) and size-exclusion chromatography (SEC)—have also been employed, but these likewise fail to achieve complete removal of bovine EVs from FBS [18].

Commercial Exosome-Depleted FBS: Convenience at the Cost of Uncertainty

To circumvent the burdens of in-lab depletion, commercially available exosome-depleted FBS products have emerged as an attractive alternative. These products claim to remove over 90% of endogenous EVs while maintaining serum performance in cell culture, offering improved workflow consistency and reliability. Some employ proprietary ultrafiltration techniques to preserve growth factors more effectively than UC. However, this convenience comes with multiple fundamental concerns.

First, the depletion methods are proprietary and opaque. Manufacturers rarely disclose the specific protocols used, making it difficult for researchers to fully understand the composition of the final product—a black box issue that undermines transparency [19]. Second, batch-to-batch variability remains. FBS is an

inherently variable biological product, and this variability persists even after exosome depletion, potentially compromising experimental reproducibility [15]. Third, residual contaminants are not completely eliminated. Despite manufacturers' claims, commercial products still contain detectable levels of bovine EVs, RNA, and other nanoparticles [15].

Fourth, alterations in serum composition are inevitable. Regardless of the method used, depleting exosomes also affects non-vesicular serum components. For example, levels of growth factors such as FGF may be reduced, potentially influencing cell behavior [19].

Most critically, these interim solutions introduce a new confounding factor: the depletion artifact. Processing FBS to remove exosomes—whether via UC or commercial filtration—does not simply create exosome-free serum; it yields a biochemically altered material. UC, in particular, not only removes exosomes but also reduces essential nutrients, which may stress cultured cells and consequently affect their exosome secretion and cargo profiles [15]. One study found that cells cultured in commercial exosome-depleted FBS required lower serum concentrations than those cultured in UC-depleted FBS, suggesting that UC causes greater damage to the serum's nutritional profile [15]. Consequently, direct comparisons between standard FBS and UC-depleted FBS in experimental designs are not single-variable experiments. At a minimum, two factors are altered: (1) the presence or absence of bovine EVs, and (2) the concentration of other biologically active serum components. Thus, findings from such comparisons may be misinterpreted. Observed changes in exosomal cargo or function may not reflect the absence of bovine exosomes per se, but rather cellular stress responses to nutrient depletion. This highlights a significant methodological flaw and strongly suggests that these stopgap approaches are inadequate for rigorous and reproducible science—let alone clinical translation.

A Paradigm Shift Toward Chemically Defined Media

The inherent limitations of interim solutions underscore the need for a fundamental paradigm shift in culture systems used for exosome research and production. This shift points toward the adoption of chemically defined media (CDM)—formulations in which all components are known and controllable. To understand the significance of this transition, it is first essential to clarify several often-confused terms related to culture media, which continue to contribute to ambiguity and reduced reproducibility in the field [20].

Dissecting the Terminology of Modern Cell Culture

Ambiguous terminology in describing culture media remains a major source of confusion and reduced reproducibility in exosome research [20]. To promote clarity, transparency, and standardization, it is essential to define key terms based on their compositional characteristics and regulatory implications. SFM refer to formulations that exclude whole serum but may still contain undefined animal-derived components such as purified albumin, hormones, or bovine pituitary extract (BPE). The inclusion of BPE—a complex and poorly characterized mixture of growth factors—can introduce extracellular vesicles and other confounding elements, thereby undermining the original goal of removing FBS [21]. While SFM represent an important step toward minimizing serum-associated variability, their undefined components still pose challenges in the context of exosome research. To address the residual variability in SFM, XF media were introduced as a step forward. These media exclude components derived from non-human animals, thereby eliminating some sources of immunogenicity and contamination. However, they frequently incorporate undefined human-derived supplements such as human serum albumin (HSA) or human platelet lysate (hPL), which continue to introduce biological variability and potential contaminants [22-24]. As a result, XF media reduce but do not eliminate the uncertainty associated with complex biological inputs. To further minimize such variability, researchers have turned to animal component-free (ACF) media, which adopt a more stringent definition by excluding all substances derived from both human and non-human animal tissues. Proteins and growth factors in ACF media are typically recombinant, reducing the risk of direct biological contamination. However, the manufacturing processes for these components may still involve the use of animal-derived materials, raising concerns about indirect contamination and batch-to-batch inconsistency. Ultimately, the only media type that fully addresses these concerns is CDM. Often considered the holy grail of the field, CDM consist exclusively of known components with precisely defined concentrations. These media contain no serum or tissue extracts, and all proteins—such as albumin and growth factors—are recombinant and highly purified. By eliminating the variables associated with unknown constituents and biological variability, CDM provide maximal transparency, reproducibility, and suitability for both basic and translational exosome research [25]. Distinguishing between these terms is essential for ensuring experimental clarity and standardization. Table 1 provides a comparative summary of the key characteristics associated with each media formulation.

Fundamental Challenges in Developing Universal Chemically Defined Media

Despite their conceptual appeal, the development of a universal, one-size-fits-all CDM remains a formidable challenge [26]. Several key factors contribute to this difficulty.

One major obstacle lies in the cell-type specificity of metabolic and nutritional requirements. Different cell lines and primary cells exhibit unique and complex demands that are not easily met by a single formulation. For example, media optimized for Chinese hamster ovary (CHO) cells may be inadequate for human MSCs, and even organoids derived from different tissues require distinct combinations of growth factors to support their growth

Table 1. Glossary of culture media formulations used in cell-based exosome research

Characteristics	Serum-based media	Serum-free media (SFM)	Xeno-free media (XF)	Animal component-free media (ACF)	Chemically defined media (CDM)
Definition	Traditional media supplemented with whole animal serum (mainly FBS).	Does not contain serum but may include undefined animal-derived components such as purified proteins or tissue extracts.	Excludes non-human animal components but may contain human-derived supplements such as human serum albumin (HSA) or human platelet lysate (hPL).	Excludes primary substances derived from human and non-human animal tissues. Uses recombinant proteins, though animal-derived materials may be used in the manufacturing process.	All chemical components and their concentrations are precisely known. All proteins are recombinant and highly purified.
Representative Components	Basal media + 5–20% FBS	Basal media + BPE, purified albumin, insulin, etc.	Basal media + HSA, hPL, recombinant growth factors, etc.	Basal media + recombinant proteins (manufacturing process may not be fully disclosed)	Basal media + recombinant albumin, recombinant growth factors, synthetic lipids, and all defined components
Variability/ Contaminants	Bovine EVs, exogenous RNAs, protein aggregates, prions, viruses, and severe batch-to-batch variability [9]	EVs and undefined factors from BPE, lipids bound to albumin [20]	Risk of human pathogen transmission, variability between hPL/HSA batches [24]	Potential contamination from animal-derived materials used in secondary ingredients or manufacturing	None (theoretically the lowest) [25]
Regulatory/ Clinical Implications	High risk and regulatory barriers for clinical applications [26]	Preferred over serum-based media, but undefined components still pose regulatory concerns [20]	Improved safety profile over FBS, but variability and safety issues remain with human-derived materials	Closer to clinical grade, but requires full traceability of manufacturing process	Ideal standard for clinical use and large-scale production

and differentiation [27]. Another critical barrier is the inherent complexity of serum. Serum contains a vast and not fully characterized mixture of growth factors, hormones, lipids, and transport proteins. Reproducing this supportive environment with a limited set of known, defined chemicals is an enormous undertaking [9]. While CDM aim to reduce variability by excluding undefined components, this also removes many of the beneficial, though unidentified, bioactive factors found in serum. Additional economic and practical limitations hinder the development of CDM. Tailoring and optimizing a defined medium for each specific cell type is labor-intensive, costly, and time-consuming. Despite its shortcomings, FBS has historically delivered reliable performance across diverse applications, which has delayed the widespread adoption of more stringent but technically demanding alternatives. Moreover, regulatory hurdles complicate this process. While regulatory agencies increasingly demand serum-free processes for clinical safety, the absence of standardized definitions and frameworks for media composition makes it difficult for newly developed formulations to gain regulatory approval as ancillary materials in cell and gene therapies.

Collectively, these challenges give rise to what has been described as the purity–performance trade-off. As the degree of chemical definition increases—progressing from serum-based media to fully defined formulations—there is often a corresponding decrease in initial cell performance. One study explicitly noted that many formulations exhibit reduced performance at higher levels of chemical definition [28] Similarly, in the case of CAR-T cell production, media based on FBS and its complex mix of growth-promoting factors have outperformed currently available CDM [29]. At the heart of this trade-off lies the extraordinary biochemical richness of serum. Our understanding of cellular metabolism remains incomplete, and attempts to recreate the supportive environment from the ground up using only known components may fail to account for critical but as yet unidentified factors present in serum. This highlights a key insight: the development of high-performance CDM is not simply a matter of substituting recombinant versions of known serum ingredients, but rather a deeper, discovery-driven process aimed at identifying all factors essential for optimal cell health and productivity. It is at this frontier that advanced technologies such as high-throughput screening (HTS) and artificial intelligence (AI)—discussed in Section 4—are poised to accelerate discovery and help overcome the purity–performance trade-off that currently constrains the field.

Advances in Chemically Defined Media for Therapeutically Relevant Cell Types

Despite the theoretical challenges, the development of CDM for exosome production has made significant progress, particularly in the context of key therapeutic cell types such as MSCs and epithelial cells. These advancements not only address the issue of contamination but also open new avenues to actively enhance the therapeutic potential of exosomes.

Enhancing Exosome Production from Mesenchymal Stem Cells

MSCs are a central resource in regenerative medicine, and exosomes derived from these cells have shown great promise in promoting tissue repair and immunomodulation [6,7]. Accordingly, the development of CDM tailored for MSC culture has emerged as a critical area of research. Traditionally, MSCs have been cultured in media such as low/high glucose DMEM or α-MEM supplemented with 10–20% FBS or hPL. However, these approaches inherently carry the contamination and variability issues discussed earlier. In response, several commercially available CDM products specifically designed for MSC culture and exosome production have recently become available.

Oxium™EXO is a chemically defined, xeno- and blood component–free medium that reportedly increases the secretion of small EVs from MSCs by more than threefold compared to standard DMEM [30]. Representative examples of these and other chemically defined media are summarized in Table 2. It supports cell viability and maintains the stem cell phenotype while enriching for vesicles within the 51–200 nm range. CellCor™ CD MSC and CellCor™ EXO CD are animal component– and serum-free chemically defined formulations composed of over 200 known ingredients. These media are designed to support stable MSC proliferation and extracellular vesicle (EV) production while completely excluding serum-derived impurities. Studies have shown that not only do these CDM enhance EV yield, but they also improve regenerative cargo profiles—such as those modulated by melatonin co-treatment [31]. RoosterBio High Performance Media XF is another xeno-free medium developed for rapid and large-scale MSC expansion. This formulation aims to reduce both production costs and regulatory burdens by supporting efficient MSC growth in a defined, serum-free environment.

Importantly, culturing MSCs in CDM offers more than just a way to eliminate contaminants. It also allows for the controlled enhancement of therapeutic properties. For instance, CDM can help maintain cell health during EV harvesting, avoiding stress-induced artifacts often associated with serum starvation protocols. Moreover, the defined composition enables intentional modulation of EV cargo by adding specific small molecules or biologics [31].

Culturing Epithelial Cells in Defined Environments

Epithelial cells are also of growing importance in both research and clinical applications and face similar challenges in the pursuit of producing pure and functional EVs.

In one investigation, primary bovine mammary epithelial cells (pbMECs) and the MAC-T epithelial cell line were successfully cultured in an FBS-free, chemically defined medium. The formulation consisted of DMEM/F12 supplemented with B27, insulin, hydrocortisone, estradiol, progesterone, and epidermal growth factor (EGF) [32]. This study not only demonstrated a feasible serum-free recipe for epithelial cells but also emphasized the need to optimize EV isolation protocols accordingly. The combination of ultrafiltration, size-exclusion chromatography, and ultracentrifugation (UF-SEC-UC) was identified as the most effective method for EV recovery. Studies on human amniotic epithelial cells (hAECs) have further shown that different CDM formulations significantly influence EV production. Critically, cell viability and proliferation are not reliable predictors of EV yield [33]. Instead, CDM choice directly affects the EV proteome and the levels of key markers such as tetraspanins. These findings suggest that media optimization must focus specifically on EV production

Table 2. Summary profiles of selected chemically defined media developed for exosome production

Media	Target cell type	Reported definition level	Key known components/ Supplements	Reported impact on EV production	Ref.
Oxium™EXO	Human mesenchymal stem cells (hMSCs)	Chemically defined, XF, Blood-Free	Proprietary patented formulation	>3-fold increase in yield, enrichment of 51–200 nm particles, maintained cell viability	[30]
CellCor™ EXO CD	Human mesenchymal stem cells (hMSCs)	Chemically defined, ACF, Serum-Free	Over 200 defined ingredients	Excludes serum-derived impurities, promotes EV production, enhances regenerative miRNA cargo with melatonin	[31]
RoosterBio HPM-XF	Human mesenchymal stem cells (hMSCs)	Xeno-Free (XF)	Proprietary formulation	Designed for rapid, large-scale hMSC expansion, reducing cost and regulatory burden	
Custom pbMEC Medium	Primary bovine mammary epithelial cells (pbMECs)	Chemically defined, FBS-Free	DMEM/F12, B27, insulin, hydrocortisone, E2, P4, EGF	Enables pure EV isolation without FBS contamination, effective when combined with UF-SEC-UC separation method	[32]

rather than general cell growth performance. Other examples underscore the need for careful evaluation of media marketed as serum-free. Many of these still contain undefined additives like BPE, which can reintroduce variability and contamination risks. Therefore, scrutinizing product composition remains essential [21].

Collectively, these advancements reveal that media formulation is not merely a passive support system for cell survival but rather an active regulator of exosome biology. The hAEC study provides compelling evidence: although different CDM support similar levels of cell proliferation, they produce EVs with distinct proteomic signatures and marker profiles—suggesting that EV production and cell proliferation are, in fact, separable processes. Furthermore, the study in which melatonin was added to CDM to enhance the regenerative miRNA cargo of MSC-derived EVs clearly demonstrates that defined culture conditions enable intentional and tunable control over therapeutic EV characteristics [31]. Together, these findings indicate a shift in the exosome therapeutics paradigm—from merely producing pure exosomes to engineering designer exosomes with tailored functions. In this context, the culture medium is no longer just a background variable but becomes a central biomanufacturing tool for engineering the final therapeutic product. Thus, the development of CDM should be viewed not just as a means to eliminate contaminants but as a strategic opportunity to optimize therapeutic cargo.

Future Directions in Media Development and Optimization

The development of CDM requires moving beyond traditional one-factor-at-a-time optimization strategies toward systematic and data-driven approaches. Future progress will rely on the integration of high-throughput screening (HTS), statistical experimental design, and artificial intelligence (AI) to accelerate the discovery and refinement of next-generation media formulations.

High-Throughput Screening and Design of Experiments: Systematizing Media Discovery

HTS and design of experiments (DoE) methodologies make it possible to vary multiple components simultaneously and test hundreds or even thousands of media formulations in parallel [34]. This strategy is critical for navigating the complex and multidimensional design space inherent to multi-component CDM development. These approaches are facilitated by miniaturized and automated cell culture platforms, such as 96-deep well plates, microarrays, and microfluidic systems [35]. Combined with robotic liquid handling and automated imaging technologies, they allow for rapid, high-resolution acquisition of performance data and streamlined optimization workflows [36].

Among the DoE strategies, media blending has emerged as a particularly effective approach. By mixing multiple base media in varying proportions, researchers can generate a wide array of novel formulations and rapidly identify optimal concentration ranges for multiple factors within a single experiment. This method has proven successful in fed-batch CHO cell cultures and holds promise for improving exosome production [34].

The Rise of In Silico Formulations: AI and Computational Modeling

The most advanced developments in media optimization are now taking place in silico, where computational tools are used to design and refine media compositions with minimal reliance on traditional lab-based screening. AI and machine learning (ML) platforms are capable of integrating large-scale omics data—including genomics, proteomics, and metabolomics—to model cellular responses and predict optimal nutrient and signaling conditions [37]. These predictive models can be tailored to specific cell types or production goals, enabling rational media design guided by data rather than intuition [38].

ML pipelines are particularly well suited for optimizing media for primary cells with high donor-to-donor variability, such as T cells. By building individualized models for each donor, ML can outperform conventional statistical methods in predicting proliferation and viability, enabling one-time optimization. Similar approaches are directly applicable to MSCs, where inter-donor heterogeneity is also a major concern. Hybrid ML frameworks are additionally being developed to predict critical quality attributes (CQAs) of therapeutic products, such as protein charge variants, and could be extended to forecast exosome cargo profiles and functional properties [37]. AI technologies are increasingly being embedded into automated cell culture platforms, such as CellXpress.ai, which provide real-time monitoring and decision-making capabilities for media supplementation, passaging, and harvesting. These systems reduce operator variability and standardize culture conditions, thereby improving consistency, scalability, and regulatory compliance.

Collectively, these computational and automation tools significantly reduce development timelines, lower experimental costs, and improve the yield and predictability of final products. Given the complexity of cell-specific nutritional requirements and the active role of media composition in determining exosome function, traditional trial-and-error approaches are no longer sufficient. The ultimate goal is to solve a high-dimensional optimization problem—identifying the optimal combination of dozens or even hundreds of components that maximize the yield and therapeutic potency of exosomes carrying defined molecular cargo. Technologies such as HTS, DoE, and ML are uniquely positioned to address this challenge, enabling exploration of large parameter spaces and the construction of predictive models that go beyond human intuition. The physical realization of this paradigm is found in AI-powered automated culture systems, which represent a fundamental shift in exosome manufacturing from a biological to an engineering-driven discipline. As exosome therapeutics evolve, success will depend on the ability to integrate biotechnol-

ogy, data science, and automation. Those who effectively deploy these interdisciplinary tools will lead the development of the next generation of high-potency, high-quality, and scalable exosome-based therapies.

CONCLUSION

This review has examined the evolution of cell culture media strategies for the production of therapeutic exosomes, highlighting the ongoing transition from serum-dependent and poorly defined systems to highly controlled, chemically defined environments [9]. Several key conclusions emerge from this analysis. First, interim approaches such as ultracentrifugation or commercially depleted sera are insufficient for clinical-grade applications. These strategies fail to ensure the purity and consistency required for therapeutic use and often introduce experimental artifacts that complicate data interpretation [15]. Second, the consistent and standardized use of media-related terminology—such as SFM, XF, ACF, and CDM—is essential for ensuring transparency, reproducibility, and meaningful cross-study comparisons in the field [20]. Most importantly, cell culture media must no longer be viewed as passive scaffolds for cell survival, but rather as active biomanufacturing tools that influence the yield, purity, and therapeutic cargo of exosomes [31]. This reframing shifts the goal of media development from simply removing contaminants to intentionally engineering exosome function. Ultimately, the successful clinical translation and commercial-scale production of exosome therapeutics will hinge on continued innovation in robust, scalable, and fully chemically defined media. Addressing this challenge requires a multidisciplinary convergence of cell biology, high-throughput automation, and artificial intelligence. Such an integrated approach holds the key to realizing precision-engineered exosome therapies and opening new frontiers in regenerative medicine and personalized healthcare.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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