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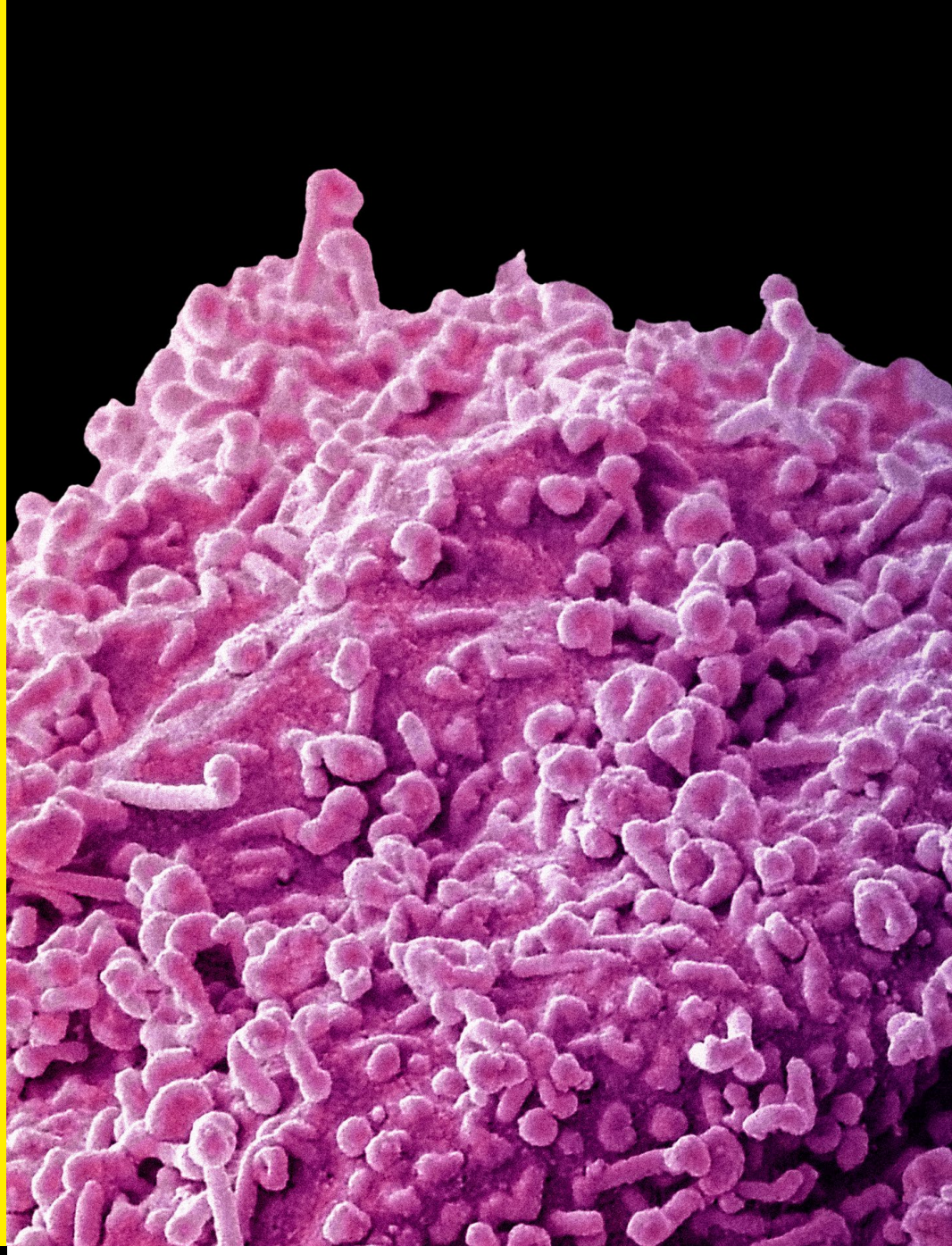


Innovating Now for the Future of EV Therapeutics

July 7, 2026 | Aslan (Mehdi) Dehghani, Tiffany Pogue, Mukund Srinivasan

Editorial

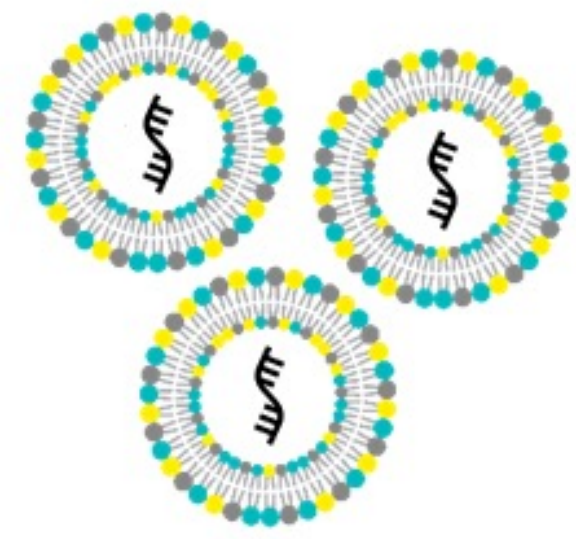
The discovery of extracellular vesicles (EVs) by Harding and Heuser more than thirty years ago has propelled advancements in therapeutic development.

As of January 2026, there are over 300 EV-based drug candidates for a range of indications, such as cancer, CNS/neurology, inflammation, and pulmonary diseases. While no EV therapy has achieved commercial approval, three drug candidates are currently in Phase III clinical trials, potentially paving the way for the first approved EV therapies and marking a pivotal moment reminiscent of cell and gene therapy breakthroughs two decades ago.[1]

This emerging therapeutic modality is advancing rapidly, positioning EVs within a new era of biologically engineered therapeutics. But its progress is hampered by several foundational challenges the industry needs to overcome. In this article, we will review the current state of this therapeutic modality and explore three primary challenges.

The EV Revolution: Innovation, Momentum, and Versatility

The main approaches to produce EVs can be classified as intrinsic (or naïve) and engineered. Intrinsic EVs are naturally secreted by various cell types and retain the biological properties of their cell of origin. Among these, mesenchymal stem cell (MSC)–derived EVs are the most common and are widely used for regenerative medicine applications. In contrast, engineered EVs are intentionally modified—either by manipulating the source cells or by externally loading the vesicles with specific cargo(s)—to enhance or tailor their therapeutic function. Intrinsic EVs are currently dominating the EV pipeline, however modifying extracellular vesicles (EVs) is rapidly gaining traction in the therapeutic field due to their ability to enhance targeted delivery while minimizing toxicity.

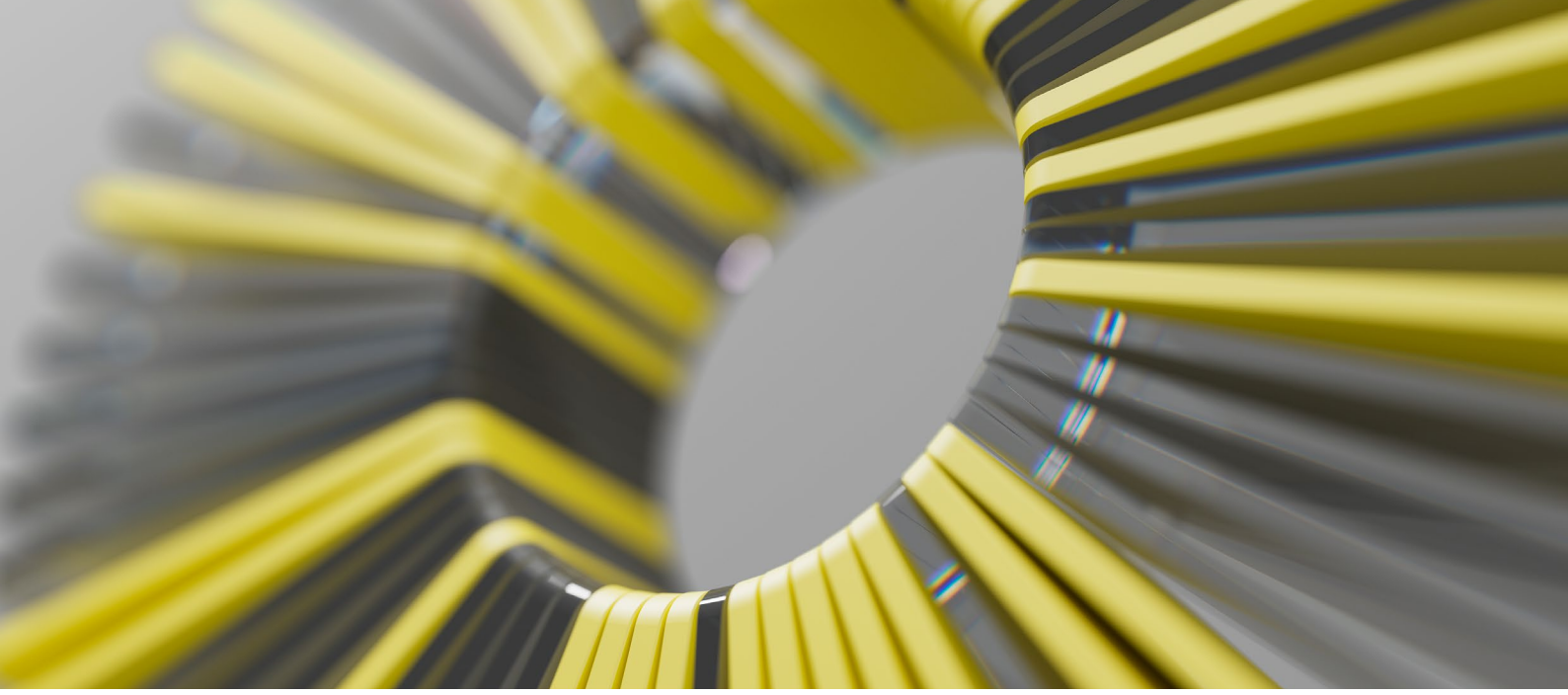


Cargo loading or engineering is achieved by modifying EVs internally or externally for delivery applications. Two primary approaches are employed to load cargo into EVs: endogenous (cell-based) methods and exogenous (post-isolation) techniques.[2]

Endogenous cargo loading utilizes the biological machinery of donor cells to incorporate specific molecules into EVs during their formation. By engineering or modifying these cells, desired cargos such as siRNA, miRNA, and proteins are packaged into vesicles during biogenesis, resulting in functional and targeted EVs. Several strategies are commonly used within this approach:

- **Genetic Engineering:** Donor cells are engineered via plasmid- or lipid-based transfection, or transduced with viral vectors, directing them to produce specific proteins or RNAs. These molecules are then sorted and packaged into EVs by the cell's own mechanisms.
- **Co/Incubation or Drug Exposure**: Cells are exposed to particular drug compounds, which influence the inclusion of selected cargo within EVs.
- **Direct Parental Cell Manipulation:** Techniques such as electroporation are used on donor cells to introduce therapeutic cargos, which are subsequently loaded into vesicles as they are formed.[3]

Exogenous cargo loading involves introducing therapeutic molecules into EVs after they have been purified. This approach is commonly used to load proteins, nucleic acids, or other therapeutics into pre-existing vesicles. Techniques include: electroporation, sonication & extrusion, freeze-thaw cycles, passive incubation, and microfluidic-based cargo loading.[4]



Three Primary Challenges in EV Development

Despite rapid progress, several critical barriers continue to limit the full realization of EV-based therapies. First, the field has a technology gap with respect to accurate characterization of EVs. Second, as the market catches up to technology and innovation, regulatory guidelines are constantly evolving to stay up to date. Without a gold standard framework, developers face uncertainty around what constitutes sufficient product quality, safety, and consistency. Finally, development and manufacturing challenges, such as process reproducibility and scalability, are embedded throughout the product lifecycle. Addressing these issues is critical to the commercial viability of therapeutic candidates.

Characterization

As cells secrete extracellular vesicles (EVs) into the culture supernatant, one of the major challenges in EV bioprocessing is understanding and monitoring the composition of the conditioned medium, particularly the relative abundance of EVs and co-existing impurities. This complexity is further compounded by the presence of multiple EV subpopulations, including microvesicles and exosomes, with the latter often considered the most relevant for therapeutic applications. EVs are inherently heterogeneous in size, membrane composition, and molecular cargo, and their distinction from non-vesicular extracellular particles (NVEPs) remains a significant analytical challenge due to overlapping size ranges and similar biophysical properties.[5]

Reliable EV characterization remains one of the key bottlenecks in the field, largely due to EV heterogeneity and the lack of sufficiently sensitive and specific analytical tools. Current EV characterization methods can be broadly categorized into bulk and single-particle analytical techniques. Bulk methods—including Western blotting, ELISA, qPCR, proteomics, and lipidomics—provide average properties of the overall sample population. While these techniques are useful for confirming the presence of EV-associated proteins, nucleic acids, and lipids, they do not provide information on individual particles or population heterogeneity.

In contrast, single-particle analysis techniques such as nanoparticle tracking analysis (NTA), high-resolution flow cytometry, resistive pulse sensing, single-particle automated Raman trapping analysis (SPARTA), and electron microscopy enable the analysis of individual particles within a heterogeneous EV population. These methods provide insights into particle concentration, size distribution, morphology, and, in some cases, surface marker expression. However, they can suffer from low specificity towards EVs which can make process optimization more challenging and signifies the importance of orthogonal analytics.

Analytical chromatography is one orthogonal analytical approach that has emerged as a valuable tool for process development and optimization. For example, multi-detector platforms such as PATfix® coupled with analytical size exclusion chromatography (SEC) enable separation and real-time characterization of EVs and co-isolated soluble impurities within conditioned media or process intermediates. Such systems provide a powerful means to monitor impurity removal and EV retention across each downstream processing unit operations, thereby facilitating process optimization and improved product quality.

Currently, there are no universally accepted characterization methods for EV therapeutic development, leading to a confusing regulatory pathway for this modality.

Regulatory Guidelines

The regulatory approval of EV therapeutics remains a significant challenge because EVs exist at the intersection of biologics, cell-derived products, and advanced therapeutic modalities, where regulatory expectations are still evolving and not yet fully standardized. Currently, there are no universally accepted characterization methods for EV therapeutic development, leading to a confusing regulatory pathway for this modality. In light of the challenges in identifying and separating EV particles of interest, industry leaders should advocate for validated characterization techniques. Concurrently, clear guidance on quality control and standardized frameworks for EV-based therapies must be established.[6]

Over the past two decades, professional scientific societies have played a pivotal role in advancing new therapeutics into the clinic by establishing best practices and industry standards through advocacy, education, and training. Most notably, the International Society of Extracellular Vesicles (ISEV) collaborates with leading trade organizations, including the International Society for Cell & Gene Therapy (ISCT), to support the clinical translation of emerging therapies.

In 2014, ISEV released the Minimal Information for Studies of Extracellular Vesicles (MISEV). These guidelines highlight EV heterogeneity, encourage use of both enriched and depleted markers, recommend testing non-EV fractions to recognize whether the therapeutic effect is attributed to the EV particles and not other materials, and notes that while examples focus on mammalian systems, the principles broadly apply across organisms.

Revised in 2018 to further support the scientific advancements in the field, the guidelines "updated the topics of nomenclature, separation, characterization and functional analysis, integrating the contributions of over 380 ISEV members, a strong tribute to the commitment of ISEV members." The most recent update in 2023, "provide updated standards for conducting and reporting research on extracellular vesicles (EVs), emphasizing rigor, reproducibility, and transparency in the field." Future updates are expected to focus on expanding standardization efforts, advancing regulatory and translational discussions, and refining critical areas of extracellular vesicle development, including EV characterization, potency assays, in vivo studies, isolation methods, and therapeutic manufacturing considerations.[7]

Despite these efforts and industry advancements, gaps in regulatory guidelines remain. ISEV-TRA committee, Exosome Therapeutic Series of ISCT and Partnership for Therapeutic EVs (PTEV) have focused on translation and on bridging this gap by uniting industry, academia and regulatory bodies.

Development & Manufacturing

As with all ATMPs, EV developers must design bioprocesses that are reproducible, scalable, and cost-effective to support successful therapeutic commercialization. Addressing these challenges depends on optimizing EV processing early in development and defining a clear commercialization roadmap from the start.

- **Yield:** Achieve high productivity through robust process optimization in the preclinical phase, leveraging high-performing raw materials and consumables during EV expansion and purification.
- **Purity:** The degree of purity required depends largely on the intended therapeutic indication and how the final EV product is defined. For a pure EV product, it's critical to ensure removal of free soluble molecules as well as non-vesicular extracellular particles.
- **Reproducibility:** Support process reproducibility with consistent, defined, GMP-grade raw materials, combined with automated, closed systems that reduce human error and risk of contamination.
- **Scalability:** Implement scalable automated platforms combined with both predictive and retrospective analytics, develop reliable, consolidated characterization and QC protocols, and source raw materials with a clear path from RUO to GMP to minimize revalidation during scale-up.

Taken together, these elements form the foundation to enable bioprocessing that is safe, scalable, and cost-effective. Through continued bioprocessing excellence, Sartorius is committed to helping developers advance EV-based therapeutics toward clinical and commercial success.

"Within the Corporate Research team at Sartorius, our focus has been on conducting fundamental research to develop and optimize extracellular vesicle bioprocessing workflows"

Aslan (Mehdi) Dehghani,
Manager of Nanoparticle Technologies

Advancing EV-based Therapeutics with Strategic Partnerships: Sartorius and Stellar Notch

This need for robust, scalable, and high-quality processes underscores the importance of strategic partnerships across the ecosystem. Sartorius is collaborating with SelasBio, a biotechnology company pioneering advanced therapies for traumatic brain injury (TBI). The collaboration centers on Brain Shield—an intranasal therapy that uses stem cell–derived extracellular vesicles to deliver the therapeutic payload directly to the brain. This approach aims to repair neural damage by calming inflammation and accelerating cognitive recovery, while also bypassing the blood–brain barrier, a long-standing obstacle in neurotherapeutics.

At its Center for Bioprocessing Innovation in Marlborough, Massachusetts, the Sartorius team is contributing to the production of the new therapy through a process development agreement. This includes scaling up EV production in Univessel® SU 10-L bioreactors and supporting downstream purification for therapeutic evaluation. Sartorius Corporate Research, process development, and clinical production teams bring deep expertise in EV analytics and scalable bioprocessing.

"Developing scalable bioprocesses for this therapy would be a major step forward in neurorehabilitation."

Sunandan Saha
Head of Process Development & Clinical Production Service

"Within the Corporate Research team at Sartorius, our focus has been on conducting fundamental research to develop and optimize extracellular vesicle (EV) bioprocessing workflows. The Process Development Team, along with Corporate Research and Stellar Notch teams have collaborated closely from the earliest stages of concept development through grant writing, execution, and process optimization," says Aslan (Mehdi) Dehghani, Manager of Nanoparticle Technologies.

"Our goal is to advance biomanufacturing for innovative modalities like EVs. This starts with supporting clients from grant planning and extends to clinical application. If we succeed in developing scalable processes for this therapy, it would be a major step forward in neurorehabilitation," says Sunandan Saha, Head of Process Development & Clinical Production Service.

TBI remains a major global health challenge, affecting millions - including athletes, accident victims, and military service members alike. Compared to traditional treatments that often focus on symptom management, this novel therapy could help the brain self-repair. Its shelf-stable format allows for rapid administration in emergency settings.

How Sartorius Enables End-to-End Success of EV Therapeutics

The field of extracellular vesicle therapeutics is progressing rapidly, with an increasing number of candidates advancing toward clinical translation. Yet challenges across regulatory clarity, standardized characterization, cargo-loading strategies, and scalable manufacturing continue to shape the pace and feasibility of progress. As professional societies such as ISEV and ISCT work to establish shared frameworks and best practices, the industry is moving toward the level of structure and alignment needed to support the first commercially viable EV therapies.

As a committed partner to biopharmaceutical innovators, Sartorius plays a pivotal role in enabling this progress. Through integrated technologies, advanced analytical tools, and Process Development Services for EVs, Sartorius supports developers in building robust, reproducible, and scalable workflows from early R&D through commercialization. By combining scientific expertise with end-to-end bioprocessing solutions, Sartorius helps accelerate the path toward safe, effective EV therapeutics and contributes to shaping the future of this promising modality.

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