

Short Commentary

Advancing Extracellular Vesicle Therapeutics into Clinical Trials for Central Nervous System Disorders

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Commentary

In December 2023, the US Food and Drug Administration released a draft guidance document titled “Potency Assurance for Cellular and Gene Therapy Products Draft Guidance for Industry” for public comment [1]. Potency assays are arguably the most problematic analytic release assay to develop for cell and cell derivative products, including Extracellular Vesicles (EV). EVs are produced by many cell types and harbor parent cell-specific bioactive cargoes including proteins and nucleic acids. They are unique intercellular signaling particles that can act as both the messenger and/or effector in recipient cells. We and others have shown that Neural Stem Cell EVs (NSC EVs) derived in bioreactors have therapeutic potential for treating neurological disease and Acute Ischemic Stroke (AIS). New FDA Investigational New Drug (IND) applications are being filed and specifically, we have an IND application for AIS. As the field grows, new INDs will be filed for various other therapeutic indications. In order for EV therapeutics to move efficiently through the regulatory process to approval, there is a need for more emphasis on and development of analytical assays directly related to complex and likely multimodal, mechanisms of action. Research focused on this area will lead to new disease-specific potency assays and identification of critical quality attributes.

Potency assays for EVs are essential for defining the bioactivity, quality, batch-to-batch reproducibility and stability of EV preparations and to facilitate subsequent EV use as therapeutics or carriers for cell-free therapies. Potency assays are performed as part of product release, comparability studies and stability testing. Although potency assays are just one of many important analytic assays needed to ensure progress through clinical trials, these are often the most difficult to implement. A relevant set of potency assays needs to be linked to the mechanism of action for a therapeutic. A recent study published as a preprint describes the

development of a ubiquitous enzymatic-based assay for EVs, a single-step functional analysis to predict potency and to quantitatively measure EV-bioactivity and vesicle integrity, using small-size EV samples [2]. It is highly likely that potency assays will need to be built around the mechanism of action for specific therapeutic applications and we look forward to more publications on potential potency assays in this manner.

Early-stage potency bioassays are typically based on pathophysiological mechanisms and implicated pathways in early preclinical studies to identify potential EV mechanism(s) of action. Thus, ideally there is an initiating factor(s) that creates the signal that indicates biological activity, the dose response, as well as the duration of the response, all of which must be measurable in the bioassay. In the case of a bioassay, the process requires choosing a cell line and type that is relevant to the EVs mechanism of action. If there are multiple mechanisms of action, this may require use of additional cell lines. Qualifying the operating conditions is necessary for any assay, including but not limited to cell density, incubation time and temperature. This will ensure a rigorous, robust and reproducible assay, as the potency assay(s) will need to be further validated for specificity, accuracy, precision and linearity throughout therapeutic development.

As AIS therapy using NSC EVs moves forward, potency assays built around the mechanisms of action will play an important role in the regulatory approval process. A good potency assay starts with an understanding of the therapeutic activity of EVs [3-5]. For example, a mechanism of action of NSC EVs for AIS and potentially any disease propagated by cell damage, is to convert damaging extracellular ATP to anti-inflammatory adenosine. Also, NSC EVs reduce pro-inflammatory C-C Motif Chemokine Ligand 2 (CCL2) levels and promote an anti-inflammatory phenotype in circulating immune cells leading to reduced stroke lesion size and improved functional recovery. NSC EVs suppress multiple cell death signaling cascades in the central nervous system microenvironment. Cellular and/or acellular assays will translate these in vivo mechanisms of action to a quantifiable and reproducible output to ensure potency of each NSC EV lot.

Beyond AIS, one of the most promising applications of NSC EVs is in the treatment of Amyotrophic Lateral Sclerosis (ALS). ALS is a neurodegenerative disease that affects the motor neurons in the brain and spinal cord. In a preliminary study, we have shown that NSC EVs significantly preserved motor function, decreased serum neurofilament light chain and prolonged survival in ALS mice. NSC EVs also reduced inflammatory mediators TNF α , IL-1 β , IL-6, RIPK1 and NLRP3 in the lumbar spinal. These results suggest that NSC EVs have the potential to be developed as a therapeutic for ALS. The complex pathogenesis in the central nervous system during ALS suggests the need to develop drugs with multimodal therapeutic action and will likely require the development of multiple potency assays relevant to the active agents in and on the surface of the NSC EVs.

NSC EVs are under development as a therapeutic for neurodegenerative diseases and AIS. The therapeutic activity of NSC EVs has been demonstrated in vitro as well as in multiple AIS models. We are building on these findings to develop robust potency assays in an effort to avoid the translational pitfalls many cell therapies have encountered in clinical trials. Further studies are needed to determine the safety and efficacy of NSC EVs in humans and will be guided by advances in understanding how the therapeutic EVs act in these specific diseases. Relevant potency assays based on mechanism of action will be essential for the progression of NSC EV therapies through the clinic to the patients that need them.

Keywords: Acute Ischemic Stroke; Extracellular Vesicles; Gene Therapy; Neural Stem Cell

Conflict of Interest

The authors have no conflict of interest to declare.

References

1. United States Food and Drug Administration Center for Biologics Evaluation and Research. 2019.
2. Potency assurance for cellular and gene therapy products. Draft Guidance for Industry. 2023.
3. Adamo G, Picciotto S, Gargano P, Paterna A, Rao E, Raccosta S, et al. Functional enzymatic assays to predict the potency of extracellular vesicles. *bioRxiv*. 2023;2023-10.
4. Webb RL, Kaiser EE, Scoville SL, Thompson TA, Fatima S, Pandya C, et al. Human neural stem cell extracellular vesicles improve tissue and functional recovery in the murine thromboembolic stroke model. *Transl Stroke Res*. 2018;9:530-9.
5. Webb RL, Kaiser EE, Jurgielewicz BJ, Spellicy S, Scoville SL, Thompson TA, et al. Human neural stem cell extracellular vesicles improve recovery in a porcine model of ischemic stroke. *Stroke*. 2018;49(5):1248-56.
6. Spellicy SE, Kaiser EE, Bowler MM, Jurgielewicz BJ, Webb RL, West FD, et al. Neural stem cell extracellular vesicles disrupt midline shift predictive outcomes in porcine ischemic stroke model. *Transl Stroke Res*. 2020;11:776-88.

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