Technological and translational challenges for extracellular vesicle in therapy and diagnosis

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Extracellular vesicles (EVs) are membrane-delimited entities that take part in a far-reaching intercellular communication signalling involved in a multitude of physiological and pathological processes. Due to their ubiquitous presence and multi-faceted roles, EVs are increasingly seen as major players in human healthcare. Recent EV research advances opened up several exciting perspectives in personalized medicine at the forefront of diagnosis and therapy with technologies evolving from bench to bedside. As a result, the number of clinical trials has significantly increased these last years, and solutions based on EVs started reaching the clinical practice for wide patient healthcare. This is the case of the ExoDx™ Prostate EPI-CE Test currently available in the diagnosis market as a non-invasive EV-based urine gene expression assay to assess prostate cancer risk. Concerning therapy, the EV-based product Bexsero®, which consists of outer membrane vesicles from *Neisseria meningitides,* has received a marketing authorization as a vaccine. Despite the excitement from EV promises and the arrival on the market of the first diagnosis and therapy solutions, technological and translational issues remain major challenges to overcome in the emerging era of EV-empowered patient healthcare.

This special issue of Advanced Drug Delivery Reviews focuses on these challenges as well as cutting-edge developments in the field. Most of the contributors for this theme issue participated to an international EV Summer School dedicated to technological and translational challenges for EVs in therapy and diagnosis. This event took place in La Grande Motte, France from September 13th to 15th,

2021 as a joint initiative of the French Society for Nanomedicine (SFNano) and the French Society for Extracellular Vesicles (FSEV), reinforcing exchanges between these two communities. At the international level, this event was supported by the Oligonucleotide Therapeutics Society (OTS) and the European Society for Nanomedicine (ESNAM). At the French national level, it received the support of ECELL France, MEARY Center, the core facility Plateforme IVETh, EVOLVE-France and Medicen. All of them were represented during the Summer school chairing one of the following sections:

- EV engineering and drug delivery;
- EV and biogenic vesicles: from characterization to *in vivo* models;
- EV imaging and diagnosis;
- Towards EV clinical translation;
- EV industrial aspects;

Consistently, these EV topics are covered in this theme issue. Concerning "EV engineering and drug delivery" Le Saux *et al* [1] focused on the challenges of loading extrinsic proteins into EVs while de Voogt *et al* [2] highlighted the challenges of assessing RNA trafficking and functional transfer mediated by EVs. An important issue for leveraging advances in EV engineering is to support comparability and data report standardization in the field as complementarily addressed by Piffoux *et al* [3] and Rankin-Turner *et al* [4]. In a related initiative, Poupardin *et al* [5] assessed adherence to Minimal Information for Studies of Extracellular Vesicles (MISEV) guidelines investigating 5,093 accessible publications concerning engineered but also native EVs.

Regarding the topic "EV and biogenic vesicles: from characterization to *in vivo* models" current challenges were addressed considering the specificities related to different therapeutic indications ranging from digestive fistulas (reviewed by Sebbagh *et al* [6]), liver diseases (outlined by Kostallari *et al* [7]) and osteoarthritis (as discussed by Boulestreau *et al* [8]). In particular, delivery challenges related to the central nervous system were overviewed by Gratpain *et al* [9]. Massaro *et al* [10] captured the most recent EV-based approaches to restore antitumor immunity with an interesting focus on CAR-T cell-derived EVs.

Concerning the topic "EV imaging and diagnosis", Špilak *et al* [11] focused on comprehensively discussing how to take profit from the snapshot of cancer cell physiological status provided by EVs to

design screening, diagnosis, prognosis and monitoring analytical tools. In a more specific view, Vidal [12] provided a review dedicated to glycosylphosphatidylinositol-anchored proteins (GPI-APs) as biomarkers of cancerous diseases. Androuin *et al* [13] focused on imaging, overviewing how current elegant imaging tools available for live imaging in the zebrafish embryo can empower the investigation of EVs dynamics, biodistribution and functions for therapeutic applications.

Regarding the topic "Towards EV clinical translation", Gupta *et al* [14] provided valuable insights on EV dosing from pre-clinical to clinical studies. In a collective consensus-based approach, a position paper was provided by the work group "Extracellular Vesicle translatiOn to clinicaL perspectiVEs – EVOLVE France"[15] gathering 44 researchers/clinicians that considered EV specificities to propose 32 recommendations for manufacturing, quality control, analytics, non-clinical development and clinical trials aiming to facilitate the transition from EV research to clinical development.

Last but not least, the topic "EV industrial aspects" was covered by the review from Grangier *et al* [16] focusing on recent advances on massive EV manufacturing based on large-scale cell culture platforms and/or cell stimulation to increase EV yield per cell. Complementarily, Staubach et al [17] focused on downstream protocols. In particular, the value of purification strategies used for viruses was discussed considering their interest for manufacturing of EV-based therapeutics.

In conclusion, this timely theme issue gathers the leading opinion of clinicians, pharmacists, engineers, chemists, physicists and biologists to compose a multi-faceted view of the technological and translational EV landscape of therapy and diagnosis. We express our sincere gratitude to all authors who contributed to this special issue of Advanced Drug Delivery Reviews. We extend our thanks to all the participants of the international EV Summer School hold in La Grande Motte, France from September 13th to 15th, 2021 for the exciting exchanges and fruitful discussions. We also thank our local host Prof. Bernard Lebleu for all the time and energy he generously invested in the event co-coordination. We are extremely grateful to Prof. Hamid Ghandehari, Editor-in-Chief and Prof. Katja Schenke-Layland, Executive Editor of Advanced Drug Delivery Reviews, for the outstanding opportunity to prepare this theme issue. We sincerely hope it will shed light on current hurdles, unravelling opportunities and highlighting solutions for the clinical translation of EV-based technologies for both therapy and diagnosis.

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