INTERNATIONAL SOCIETY for EXTRACELLULAR VESICLES

April 2021

Re: Introduction to the 'Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics' of the International Society for Extracellular Vesicles (ISEV)

Dear Sir/Madam,

Please accept this letter as an introduction to the 'Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics' of the International Society for Extracellular Vesicles (ISEV) and as an offer to provide expertise as needed on the topic of extracellular vesicles (EVs).

The 'Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics' would like to work with regulators to contribute to the development of applicable regulatory guidance. We hope to jointly accelerate achieving the ultimate goal of the safe and efficient evaluation of EVs in clinical studies and eventually developing proven EV-based therapeutics. In pursuit of this goal, the Task Force and other ISEV members can serve as a valuable expert resource for regulatory bodies.

ISEV is the leading professional society for basic researchers and clinical scientists involved in the investigation of microvesicles, ectosomes, exosomes, and all other extracellular vesicles (EVs). ISEV was founded in 2011 and is now a global society of more than 1500 members from academia, healthcare institutions, and industry. Our vision is to be the leading advocate and guide of EV research from bench to clinical translation, including the potential use of EVs as safe and efficacious therapeutics and diagnostics. ISEV established the Journal of Extracellular Vesicles in 2012. Furthermore, ISEV has recently established a memorandum of understanding with the likeminded organization, the International Society for Cell & Gene Therapy (ISCT). ISCT is also active in addressing unproven and unethical cell and gene interventions (including EV therapeutics) to promote safe and effective practices ISEV, as a not-for-profit organization will continue to organize interdisciplinary forums with relevant partners to discuss expert opinions in various areas to assist scientists and clinicians to realize the clinical potential of EVs as novel therapeutics.

The recently established ISEV 'Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics' is composed of leading global experts in the EV research and therapy field. Their experience spans academia, clinical development, industry, and regulatory affairs. The Task Force is focusing on translating relevant regulatory guidance and their application to EVs as investigational new drugs (INDs) in clinical studies and to support safe and effective EV-based treatment concepts worldwide. Furthermore, the Task Force strives to identify unproved claims of therapeutic efficacy and interventions using EVs. https://www.isev.org/page/RegAffairsTaskForce

So far, the Task Force has addressed this by issuing a publicly available patient information and safety notice with the view to draw the attention of consumers to potential safety issues with the use of unregulated EV-based therapeutics. This

document does not replace the communication between patients and their clinicians, but rather serves for information only. The document can be found at: https://www.isev.org/page/PatientInformationandSafetyNotice

Although there has been a significant increase in the number of scientific publications that describe the physiological and pathological functions of EVs, their use as a new therapeutic modality is only now being explored. The Task Force recognises that there are currently no approved EV products worldwide, and this fact has been stated in a warning letter from FDA in December 2019. While there are several ongoing clinical trials based on EV products, existing and partly harmonized international regulations may require special interpretation if applied to EV-based INDs.

A “one size fits all“ regulatory approach is unlikely to be appropriate. Instead, a case-by-case risk-based approach depending on the EV source and manufacturing processes may be meaningful for developing EV-based products. There are multiple regulatory challenges to be overcome due to the complex nature of EVs and the use of EV preparations in novel therapies, although these are expected to be comparable to human cell-based therapeutic approaches. Therefore, safety standards for cell and tissue-based products may be of use as valuable roadmaps to guide regulation of EV therapeutics.

The origin of EV-based therapeutics can go beyond human-derived materials, extending to EVs from other sources, such as animals, plants and even prokaryotes. We can provide broad expertise within our network and connections with experts who may contribute with relevant experience.

We welcome the opportunity of meeting and discussing the regulatory issues based on scientific and clinical progress associated with EVs.

Yours sincerely,

Eva Rohde

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