INTERNATIONAL SOCIETY for EXTRACELLULAR VESICLES

ISEV Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics

Chairs: Eva Rohde, Marta Monguió-Tortajada

Who we are

Chairs: Eva Rohde, Marta Monguió-Tortajada

Members:

Johnathon Anderson	Francesc E. Borràs
Benedetta Bussolati	Daniel Weiss
Edit Buzas	Dave Carter
Rachele Ciccocioppo	Owen Davies
Juan Manuel Falcón	Sunny Lee Sun Young
Bernd Giebel	Mario Gimona
Rebecca Lim	Sai Kiang Lim
Anna Nowocin	Lorraine O'Driscoll
Ilona Reischl	Xenia Sango
Hidetoshi Tahara	Wei Seong Toh
Clotilde Théry	Marca Wauben
Kenneth Witwer	Ralf Sanzenbacher

Start: 2019

Clinicians

Researchers

Authority representatives

Members: 26

Nations: 15

ISEV & ISCT members

(ISCT=International Society of Cell and Gene Therapy)

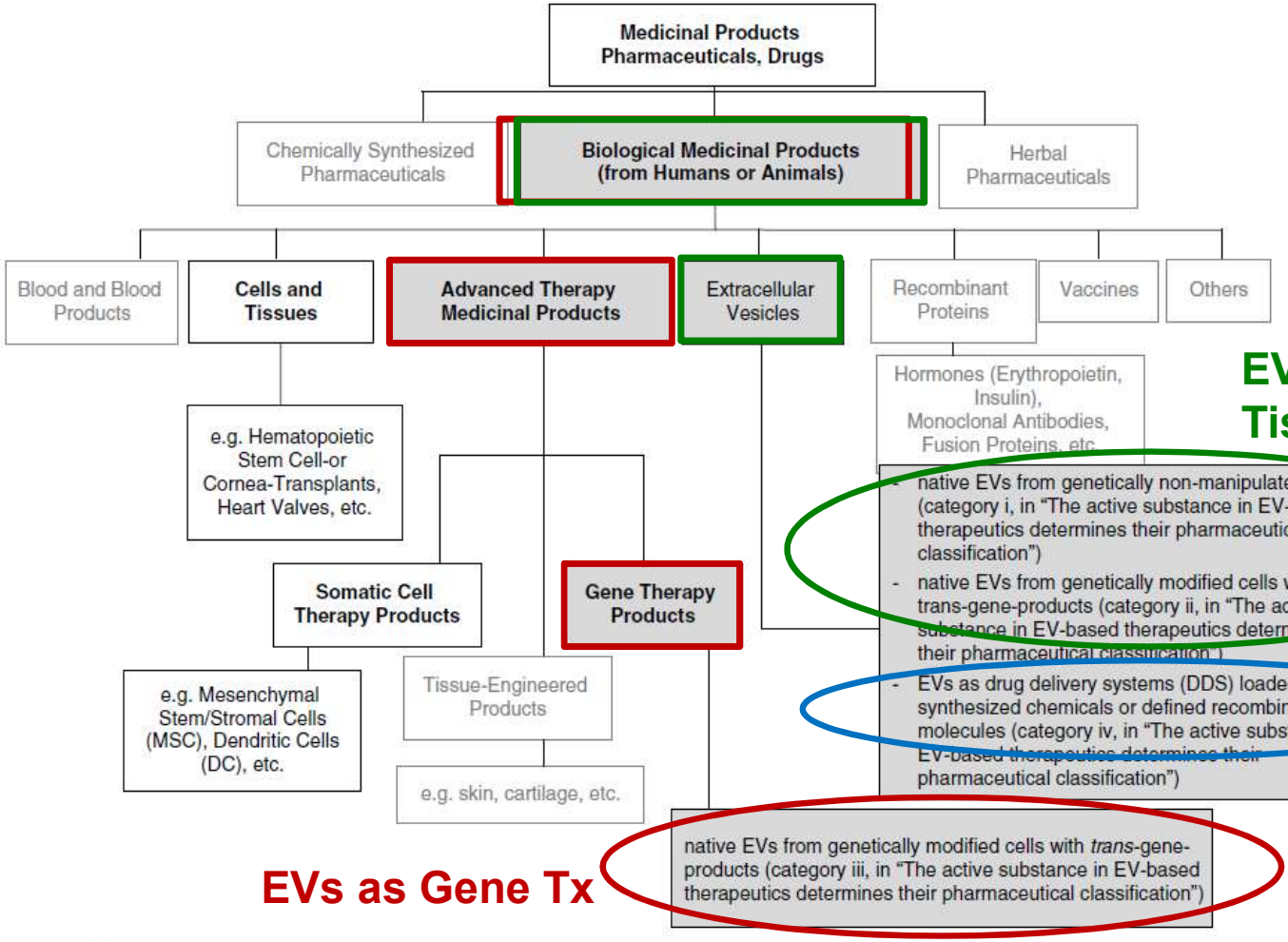
Aim

The ‘Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics‘ would like to work with stakeholders from regulatory authorities, academia, clinical research and other research institutions to contribute to the development of **applicable regulatory guidance**.

We hope to jointly accelerate achieving the ultimate goal of a **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 basic and clinical researchers and for representatives of regulatory bodies.

Mid-to-longterm activities / strategic communication

Pharmaceutical Drug Classification - Based on Proposed Biological Activity



EVs from Cells and Tissues as Tx

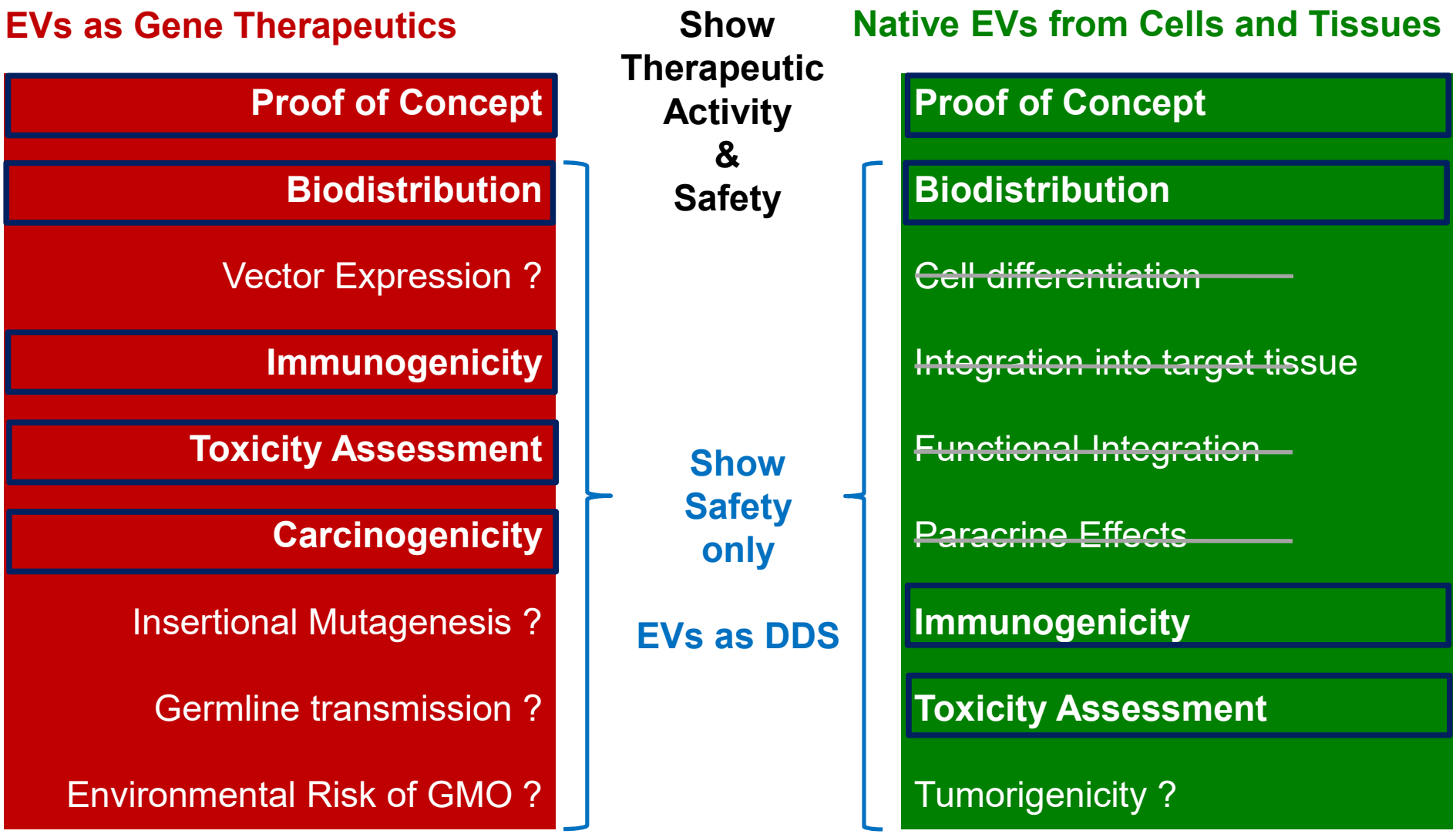
EVs as DDS
„shuttle service", not responsible for therapeutic effects

EVs as Gene Tx

Journal of Extracellular Vesicles 2015, **4**: 30087 - http://dx.doi.org/10.3402/jev.v4.30087

ISEV Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics

Non-clinical Development Plan - Inspired by the Regulations for Gene-, Cell- and Tissue-based Tx in EU



TF Activities I – mid-term

Introduction letter for regulatory authorities, clinical teams and biopharma partners

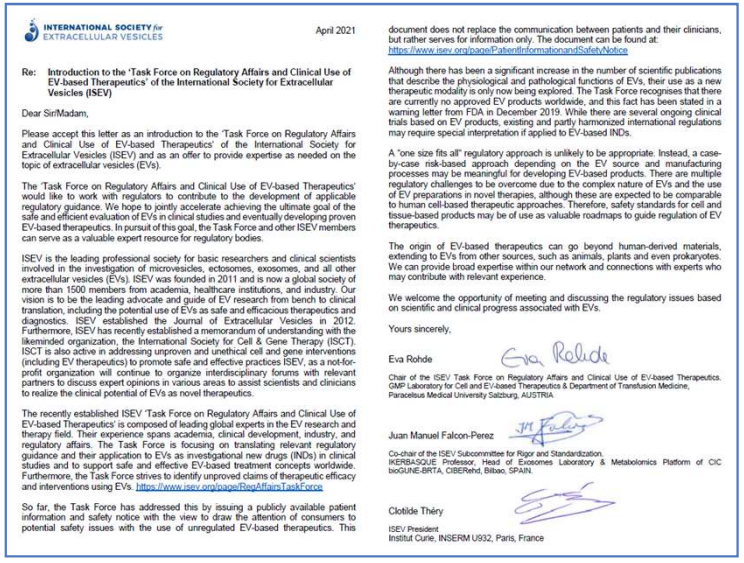
Promoting regular contact between members of the scientific EV community with regulatory authorities, clinicians, industry,…

Patient information and safety notice: extracellular vesicles/exosomes and unproven therapies

Patient outreach

MassivEVs workshop (Italy Oct 2021) participation & co-organization

Towards large scale EV production, manufacturing and good manufacturing practices (GMPs) requirements



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.

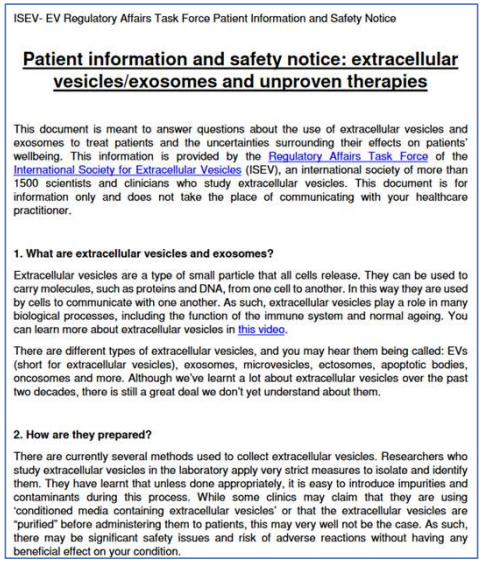
We welcome the opportunity of meeting and discussing the regulatory issues based on scientific and clinical progress associated with EVs.

Yours sincerely,

Eva Rohde
Chair of the ISEV Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics. GMP Laboratory for Cell and EV-based Therapeutics & Department of Transfusion Medicine, Paracelsus Medical University Salzburg, AUSTRIA

Juan Manuel Falcon-Perez
Co-chair of the ISEV Subcommittee for Rigor and Standardization. IKERBASQUE Professor, Head of Exosomes Laboratory & Metabolomics Platform of CIC bioGUNE-BRTA, CIBERehd, Bilbao, SPAIN.

Clotilde Théry
ISEV President
Institut Curie, INSERM U932, Paris, France



ISEV- EV Regulatory Affairs Task Force Patient Information and Safety Notice

Patient information and safety notice: extracellular vesicles/exosomes and unproven therapies

This document is meant to answer questions about the use of extracellular vesicles and exosomes to treat patients and the uncertainties surrounding their effects on patients' wellbeing. This information is provided by the Regulatory Affairs Task Force of the International Society for Extracellular Vesicles (ISEV), an international society of more than 1500 scientists and clinicians who study extracellular vesicles. This document is for information only and does not take the place of communicating with your healthcare practitioner.

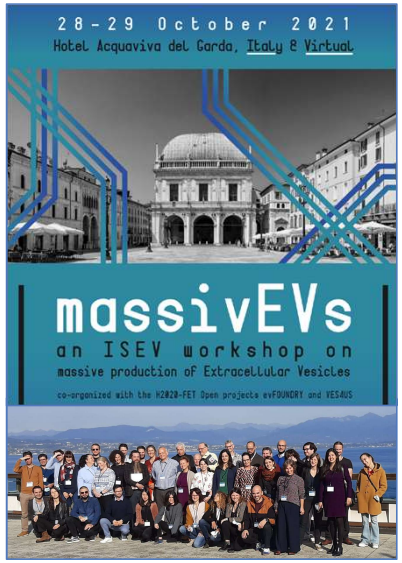
1. What are extracellular vesicles and exosomes?

Extracellular vesicles are a type of small particle that all cells release. They can be used to carry molecules, such as proteins and DNA, from one cell to another. In this way they are used by cells to communicate with one another. As such, extracellular vesicles play a role in many biological processes, including the function of the immune system and normal ageing. You can learn more about extracellular vesicles in this video.

There are different types of extracellular vesicles, and you may hear them being called: EVs (short for extracellular vesicles), exosomes, microvesicles, ectosomes, apoptotic bodies, oncosomes and more. Although we've learnt a lot about extracellular vesicles over the past two decades, there is still a great deal we don't yet understand about them.

2. How are they prepared?

There are currently several methods used to collect extracellular vesicles. Researchers who study extracellular vesicles in the laboratory apply very strict measures to isolate and identify them. They have learnt that unless done appropriately, it is easy to introduce impurities and contaminants during this process. While some clinics may claim that they are using 'conditioned media containing extracellular vesicles' or that the extracellular vesicles are "purified" before administering them to patients, this may very well not be the case. As such, there may be significant safety issues and risk of adverse reactions without having any beneficial effect on your condition.



ISEV Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics

Activities II – TF Subgroup

"Potency measurement of EV's safety and efficacy?"

Chair: A Nowocin (National Institute for Biological Standards and Control, UK)

Mission: Facilitate bench-to-bedside transfer

Focus on the (active) compound of candidate EV-Tx

- Report all biologic activities of EVs you find
- Relate them to the disease to be treated
- Tell HOW you MEASURED it
- Tell HOW you PRODUCED the EVs
- Tell HOW you can DESTROY or NEUTRALIZE the observed biologic (and potential therapeutic) activities.
- Provide biomedical context (right disease models!)
- Avoid complex cell-based assays
- Consider surrogate assays
- Search for biochemical assays

Subgroup "Potency measurement of EV's safety and efficacy"

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Focus on the (active) compound(s) of candidate EV-Tx – Mechanisms of Action – Potency Assays

Wanted:
Team of regulatory experts (EMA, FDA, PEI, AGES, MHRA, etc) and researchers (clinics, academia, industry)

NON-Goals:

Replacing rigor, common sense, or field-specific basic knowledge
Suggesting methodology independent from biomedical context
Limiting research by providing pseudo-standards
Patronizing the field
Writing the next review….
- provide encyclopedic knowledge on cell & EV biology
- summarize a comprehensive state-of-the-art in EV-Tx development

Re-inventing the wheel - pharmaceutical sciences provide required processes

Activities III – TF Subgroup

Reporting Standards for Modified Extracellular Vesicles?
Define reporting standards for modified EVs to determine therapeutic potency or improve and monitor biodistribution, targeting and cellular uptake

2022/2023:

Identify Experts – Evaluation of standards currently implemented
Identify community need for exchange
Recommendations – based on outcomes of brainstorming & exchange with various stakeholders

Presentations & organizing submeetings for special interests group discussions at ISEV, national society meetings and possibly at International Society for Cell and Gene Tx, ISCT 2023

If you feel you have something to offer the TF subgroup then please get in touch with suggestions of how you can help.

Please contact Owen Davies: o.g.davies@lboro.ac.uk

Strategic Communication I

INTERNATIONAL SOCIETY for EXTRACELLULAR VESICLES

AUTHORITIES

ISEV Task Force Introduction Letter & Contact List of Regulatory Offices and Representatives 3/2021
Systematic dissemination of Introduction Letter has started as by April 2021

PATIENTS

Patient information and safety notice: EVs/exosomes and unproven therapies
https://www.isev.org/page/RegAffairsTaskForce

SCIENTIFIC COMMUNITY

Large-scale production of EVs: report on the “massivEVs” ISEV workshop (JExBio, 2022)

Critical considerations for the development of potency assays. M. Gimona et al 2021
https://www.sciencedirect.com/science/article/pii/S1465324921000013?via%3Dihub

ISEV and ISCT statement on EVs from MSCs and other cells: considerations for potential therapeutic agents to suppress COVID-19 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7229942/

Letter Stem Cells and Development Re: "Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19" by Sengupta et al https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7374615/

2nd Letter SCD Re: Weiss Response to Sengupta et al. (DOI: 10.1089/scd.2020.0095)
https://pubmed.ncbi.nlm.nih.gov/33301389/

Strategic communication II

ISEV TF ↔ ISCT Exosome Committee partnership:

ISCT 2021 Virtual New Orleans, Plenary on Exosomes

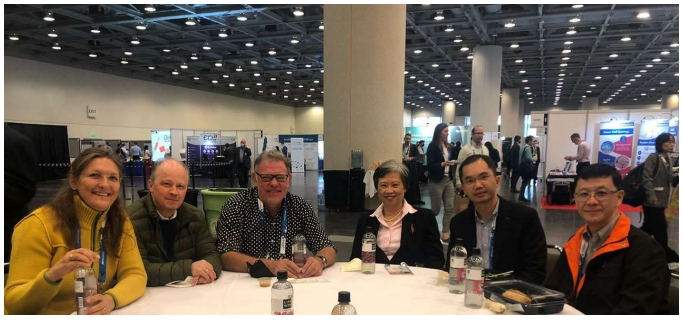
ISEV 2021, Task Force Introduction to ISEV participants

ISCT San Francisco, May 2022, Signature Series Event

ISEV Lyon, May 2022

GORDON RESEARCH CONFERENCE, Newry, Maine July 2022 / 2024 /2026

ISCT Paris 2023,…..



ISEV Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics

Thank you!

Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics

Rigor & Standardization Subcommittee

Members

26 global experts:

Clinicians, Researchers (academia and industry)

Authority representatives

15 countries represented

The Task Force is focusing on the discovery of **EV-based therapeutic strategies and their clinical translation**. The identification of the **relevant regulatory guidance** and their application to EVs as investigational new drugs (INDs) in clinical studies is a major goal as well as to **support safe and effective EV-based treatment concepts worldwide**.

The TF subgroups focus on the acceleration of translational research and clinical evaluation of EV-based therapeutics by

1) Identifying analytical tools for potency measurement of EV's safety and efficacy
2) Define reporting standards for modified EVs to enhance therapeutic potency or improve and monitor biodistribution, targeting and cellular uptake.

If you want to contribute to the ISEV - Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics with **ideas and suggestions** then please **get in touch**!!

Chair Contact Info Eva Rohde: e.rohde@salk.at
Marta Monguió-Tortajada: mmonguio@igtp.cat

More info: ISEV website