CCRM Australia:

Regulatory Workshop Extracellular Vesicles (EVs)

July 2021

Compiled minutes

CCRM AUSTRALIA

CLARITY

Commercializing Living Therapies

CCRM Australia: Regulatory Workshop on Extracellular Vesicles (EVs) Minutes

Workshop discussion topics:

- Regulatory classifications of extracellular vesicles and other considerations.
- Potency assays and concerns of quality.
- Chemistry, manufacturing, controls, and scalability.

Date & Time:	Friday, 23rd Jul 2021, 9:00 – 11:30 AEDT

Chair	● Prof Sowmya Viswanathan (University Health Network & University of Toronto, Toronto, Canada)	SV
Keynote presenters	● Professor Andrew Hill (La Trobe University) - **Breakout session I** ● Dr Sai Kiang Lim (A*STAR, Singapore) - **Breakout session II** ● Prof Luis Ortiz (University of Pittsburgh, ISCT EV Committee) - **Breakout session III**	AH SKL LO

Introductions

- ❑ Opening remarks - Silvio Tiziani (CEO) CCRM Australia
- ❑ Workshop handbook emailed to participants in advance.
- ❑ Event report capturing discussions and key points to be provided later.
- ❑ Round table introductions – SV

Cell therapy stakeholder group (CTSG) experience with Health Canada – SV; SV described the bilateral mandate of the CTSG, the engagement process for setting up agendas, meeting minutes and dissemination and the overall experience which resulted in policy changes in cell/gene therapy regulatory landscape (Deck)

Breakout session I – Landscape on considerations for regulatory classifications of exosomes.

AH provided an overview of types of EVs; introduced ISEV and the standardization efforts they have undertaken including MISEV 2014 (REF) and MISEV 2018 (REF); brief overview of TGA biologics classification scheme was provided (Deck)

- ❑ EV classification under TGA biologics was discussed
  - Are EV's class 2 if they meet definition of minimal manipulation and can be used in a homologous manner; TGA responded that burden of showing minimal

manipulation (data before manipulation = data after manipulation) would need to be provided; it was pointed out that it would not be practically feasible to generate EVs without manipulation, so data prior to minimal manipulation would be impossible to obtain

- TGA clarified that cells that are cultured or differentiated are considered Class 3, and EVs derived from such cells would also be considered Class 3

- ❑ Biologic medicines designation might be considered as an option for EV classification but need to be looked at on a case by case basis;
- ❑ There was discussion about EVs being regulated in the same way as antibodies
- ❑ There was discussion on whether a separate regulatory framework was needed for EVs as they are non-living entities; panelists clarified that other jurisdictions (FDA, Health Canada, EMA) are currently regulating EVs under existing biologics, drugs or ATP frameworks respectively, but this may evolve
- ❑ TGA clarified that diagnostic EVs are not biologics
- ❑ EVes derived from plants are not regulated as biologics, but can be regulated as biologic medicine
    - There was a deep discussion on the issue of EV heterogeneity and the requirement to consider characterization of EVs and EV cell sources; this aspect was considered similar to requirements of cell therapy products

Breakout session II – Landscape on regulatory requirements for CMC considerations for manufacturing scalable quantities of EVs including pre-clinical safety

SKL provided an overview of CMC issues surrounding EV production, EV characterization and release assays with a focus on identity and potency; international workshops organized by ISEV and ISCT and consensus from these workshops was discussed.

- ❑ Considering the previous discussion on heterogeneity, the idea of using immortalized cell lines to generate larger batches of EVs to minimize lot-to-lot heterogeneity was discussed. The risk of supporting tumour formation would need to be addressed in the EV cell source and the EVs themselves, using in vitro assays to verify any enhancements to tumour formation. MSCs as cell sources for EVs have not shown to possess tumourigenic potential, for example. TGA commented that ICH Q5D guidelines on characterizing cell lines could apply here
- ❑ Suitability of typical animal models was discussed. It was clarified that EVs as they are non-replicating would not be tumorigenic but could carry oncongenetic cargo that could promote tumour growth. Use of appropriate models (teratoma growth), in vitro assays or use of organoids would need to be carefully considered and it would be important not to simply extrapolate findings in animal models from cells to EVs. TGA when asked about appropriateness of organoids clarified that there are 3 aspects (CMC, pre-clinical toxicology and clinical efficacy) to be considered when evaluating any model
- ❑ To mitigate risk, the discussion evolved around need to fully characterize the source material (starting cell source) including assessing tumourogenic potential.

It was remarked this was easier to do with cell banks. Critical Quality Attributes (CQAs) for products will be roadmaps for determining what tests are needed for risk mitigation to project safety profile.

- ❑ Stability of EVs was discussed. EVs are inherently not stable, so the use of reference materials is not very practical. Use of biochemical analytical with widely available and recognized references standards could be used instead. ISEV has a taskforce on reference materials using meterology approach and trying to enable cross-lab standardisations. There are a few studies on counting/sizing EVs and ISEV hopes to set up guidelines around this

Breakout session III – Landscape on regulatory requirements for potency testing. LO led a presentation on the use of MSCs to treat pulmonary fibrosis and showed pre-clinical animal models that captured the effects of MSC EVs and showed mechanisms of action (Deck)

- ❑ The discussions revolved around mechanism of action and how to demonstrate this in an affordable and user friend way. There were discussions around use of animal models, in vitro culture systems. The discussion evolved to how much mechanism of action was required, especially in light of recent FDA decision on Mesoblast's MSC cell product. Ultimately potency is tested in a clinical setting and the iterative nature of this might be too late for investors and companies. Pre-clinically safety, dosing and route of administration may be answered, but mechanism of action is often not fully understood in pre-clinical studies.
- ❑ The session concluded with more discussion risk management and earlier and continued scientific discussions with regulators

Summary wrap-up

- ❑ SV expressed appreciation of speakers and participants.
- ❑ Event report covering discussions and key points to be generated.
- ❑ AH mentioned through chat about the formation of The Australia and NZ Society for EVs. Upcoming scientific meeting in November, more details of which could be found at: https://www.anzsev.org/anzsev-2021
- ❑ CCRM Australia, requested participants to share any relevant documents to be compiled and mentioned in the report and links to these are included.
- ❑ Feedback from the TGA (Here)
- ❑ Recommended article from Prof. Wojciech Chrzanowski (Here)

The Regulatory Workshop on EVs and this report was organised and prepared by the Clarity Unit, Centre for Commercialisation of Regenerative Medicine Australia

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About CCRM Australia
CCRM Australia is the Australian Hub of the highly successful Centre for Commercialization of Regenerative Medicine in Canada (CCRM). Established as a not for profit with a national focus, CCRM Australia's mission is to address bottlenecks in the translation and commercialisation of regenerative medicine discoveries in Australia, many of which have the potential to cure some of the most devastating and costly diseases in the world today.

CCRM Australia's commercially focused solutions enable businesses and research partners to achieve their commercialisation objectives by providing customised country, market and industry-specific support. To date, CCRM Australia has collaborated with researchers to advance their regenerative medicine technologies, evaluated and supported promising technologies to seek investment funding, facilitated commercialisation training and worked with international biotechnology companies to set up their clinical trials in Australia. CCRM Australia continues to do so, while providing access to resources and expertise from other CCRM Hubs around the world.

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