Clinical Potential of MSC-EVs and Translational Challenges

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Human mesenchymal stromal cells (MSCs) are a therapeutically relevant, heterogenous cell entity with immunomodulatory and pro-regenerative potentials. Apparently, MSCs mediate a huge proportion of their therapeutic effects via extracellular vesicles (EVs). Connected to several advantages in using cell-free products for the therapeutic setting, MSC-EVs emerged as promising novel therapeutic agent for various diseases, including graft-versus-host disease (GvHD), ischemic stroke, COVID-19 and sepsis.

It is our current mission to optimize the MSC-EV production strategy in a scaled, GMP compliant manner, and to set up an appropriate quality control platform to translate MSC-EVs into the clinics. One of the challenging aspects in this context is inherited from the MSC field, i.e. contradictory reports on the efficacy of MSC therapies. Apparently, not all MSC products mediate therapeutic effects when applied into patients. Similarly, we observe functional differences among independent MSC-EV preparations; even when same MSC stocks were used as starting material. Thus, to avoid draw backs as they occurred in the MSC field by failing to show efficacy in a phase III clinical trial for GvHD treatment, it is one of our most important missions to address and appropriately handle the heterogeneity aspect. To this end, we have set up a lentiviral, hTERT-based immortalisation strategy and raised MSC lines at the clonal level. EVs released by these clonally expanded immortalized MSCs (ciMSCs) reveal immunomodulatory activities and confer therapeutic activities in vivo. According to our understanding, we thus have fulfilled an essential milestone towards scaled and standardized production of MSC-EV-based therapeutics.

The next milestone to be achieved is the definition of appropriate upstream (USP) and downstream processing (DSP) strategies. For now, for the production of our MSC-EV products, MSCs are raised in 10% human platelet lysate (hPL)-supplemented media. Since sizes of hPL batches limit the scalability of our products and also challenge DSP procedures, we are currently searching for GMP-compliant media supporting both, massive ciMSC expansion as well as the secretion of potent EVs.