MESENCHYMAL STEM/STROMAL CELLS SERETOME FOR REGENERATIVE MEDICINE AND DRUG DELIVERY: PHARMACEUTICAL CHALLENGES FOR CLINICAL USE

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Mesenchymal stem cells (MSCs) play a key role in regenerative medicine, and their safety and efficacy are well established. It was initially believed that multipotency/differentiation and "homing-to-damage" properties were their mechanisms of action, but today it is shown that MSCs act also through paracrine signalling, mediated by their secretome. MSC-secretome is composed of a heterogeneous pool of bioactive molecules secreted both as free soluble factors (including cytokines, chemokines and growth factors), and as insoluble nano/microstructured-vesicles, known as extracellular vesicles (EVs). The secretome can exploit the full power of MSCs, with the advantages of an acellular therapy. Nevertheless, the clinical use is hampered from the fact that secretome is not yet a drug: for it to become one, it is necessary to produce it in industrial-scale batches, according to Good Manufacturing Practices (GMP), to convey it in a suitable pharmaceutical dosage form, to define quality requirements, and to demonstrate its safety and efficacy. In this context, some challenges have been faced and overcome: the development of a scalable GMP-compliant technological process for secretome production, its formulation in a lyophilized product, called lyosecretome, and some *in vitro* and *in vivo* tests to determine safety and efficacy.
Moreover, EVs have another highly attractive potential application: they can be used for drug targeting, as biological next-generation drug delivery systems. In fact, they intrinsically possess many attributes of an ideal drug delivery vehicle, as the ability to home damaged tissue (active drug targeting), good tolerability, stability in the blood circulation, and no immunogenicity. The therapeutic cargo can include different types of genetic material interfering RNAs, proteins, both hydrophilic and hydrophobic compounds, or chemotherapeutics when used to treat cancer. To achieve effective treatment without significant side effects, EVs can be modified to express a targeting peptide on their surfaces. The method used to load the EVs can be chosen to avoid changes to the therapeutic cargo that might decrease the efficiency of the treatment. Finally, the choice of administration route depends on the specific application of the EV drug delivery system.