Editorial

Advancing mesenchymal stem cell therapy for asthma towards clinical translation

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Although death rates due to asthma have reduced greatly in the past 30 years, asthma is still the second leading cause of death among chronic respiratory diseases (1). The burden of uncontrolled asthma is substantial and continues to grow (2). Given that a significant fraction of this burden is preventable, better management and patient adherence to therapy is critical, however this alone will not be sufficient. New therapies are urgently required that reduce the current and heavy reliance on corticosteroids and long-acting b-agonists.

Yu *et al.* present a review of the potential of one such alternative therapeutic class, mesenchymal stem cells (MSCs) and their derived products (3). MSCs' remarkable anti-inflammatory, immunomodulatory, angiogenic, antifibrotic and anti-microbial properties are in part what have driven interest in their application in regenerative medicine. As such, given asthma's pathology, it is a prime disease target for MSC-based therapy.

The review briefly details the current state of the art knowledge of MSCs' effects on asthma, allergic asthma, non-allergic asthma and occupational asthma and further, details several studies investigating the therapeutic effects of MSCs on asthma in murine models. One may wonder why the authors focus on studies employing animal models, however, incredibly, a search of clinicaltrials.gov (search last conducted 04 September 2022. Search terms: mesenchymal stem cell, MSC, asthma) lists only four MSC-related trials in humans, of which two are currently recruiting (NCT05147688, NCT05035862), one was terminated early by the sponsor (NCT03137199), and one is of unknown status given that the study has passed its completion date and status has not been verified in more than two years (NCT02192736). Despite asthma's global prevalence, associated socioeconomic burden over multiple decades, and the fact that recent trials using MSCs or MSC-derived therapies for COVID-19 number approximately 394 (source: clinicaltrials.gov, search last conducted 04 September 2022. Search terms: COVID-19 and MSC) four listed MSC trials in asthma is less than impressive.

This disparity further highlights the immediate and potentially impactful need for more focused translational work in the asthma therapeutic MSC space.

With translational research in mind, and despite the otherwise comprehensive nature of the review, it and many other publications in the field is missing a central element that will be a key determinant of MSCs' ultimate therapeutic utility, that is to say the route of administration. The most commonly used to date in both development research and clinical studies are the intravenous and inhalation routes. The easiest, most controlled route is intraveneous where a known dose is delivered in its entirety to the patient. Of the two, intraveneous administration has

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been the more commonly used across several human studies for various diseases (4-6). However, given the potential for first pass losses and non-specific targeting, the fraction of the administered dose ultimately retained in the lung is unknown, but yet is very likely low. More sensibly, for lung diseases the topical administration onto the airway epithelium may be achieved via the inhalation route. This brings the advantage of direct administration to the target site, reduced systemic exposure, and the potential for lower administered doses. Aerosol generator device selection is a key criterion, with nebulisers the most likely solution currently, given their demonstrated ability to aerosolise liquid suspensions of cells as well as their derived products, for example conditioned media and extracellular vesicles (7-9). Of further note, both the choice of nebuliser type and the patient intervention, for example, spontaneous breathing, mechanical ventilation, high flow nasal oxygen will have a significant bearing on the dose delivered to the lung (10-16). Thus, the patient type (for example adult or pediatric), clinical intervention and safety considerations at the time of MSC therapy must be considered in order to control and ensure appropriate dosing (17-20).

Some studies do however provide detailed reviews of the relative advantages and disadvantages of each of MSC and MSC-derived therapeutic delivery, by both the intraveneous and inhalation routes (21-23). Fröhlich in particular calls out some significant red flags for delivery of MSCs via the intraveneous route, such as the activation of the complement system, and the consequent risk of thrombus formation in the pulmonary vasculature and retention in filters used by extracorporeal membrane oxygenation equipment (22).

Yet another consideration in the translation from bench to bedside are the regulatory requirements for therapeutics. For reasons of patient safety, and consistency of dosing, at the bedside MSCs shall need to be dosed as part of a drug device combination product and consequently, the co-development of the cell therapy and delivery device (needle and syringe or nebuliser) shall be required from the early phases of development through to final regulatory submissions (24). At an early research level, this is understandably not a key stage gate, however, in order to maximize the clinically relevant output from the research effort to date, it must be understood and built in at an early stage in order to de-risk and possibly even expedite development.

Finally, as Yu *et al.* have pointed out, there is clearly significant potential for the application of MSCs and their by-products in the treatment of asthma however the next steps need to involve a multidisciplinary approach to advancing towards an increased number of human trials. This shall be vital in order to move MSC-based therapies closer to a clinical reality, or not, should the safety and efficacy not be shown.

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