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A Cross-Platform Challenge behind the Role of Human Mesenchymal Stromal Cells in Organ Transplantation

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Organ transplantation has become an essential treatment for saving and prolonging lives in a wide range of clinical disorders. It is a complex procedure and often convoluted by distinct issues related to clinical outcome and number of donors [1]. Recent attempts to overcome these problems have been demonstrated in the field of regenerative medicine [2]. Regenerative medicine is a branch of medicine involved in the development of methods for the regeneration and repair of tissues and organs damaged by age, diseases or congenital defects. It encompasses numerous strategies including the use of biomaterials, stem cells and bio-cues or any combinations thereof, to promote tissue healing [3]. In this context, Human Bone Marrow Stromal Stem Cells (MSCs) have proved to be an effective source for transplantation due to their capacity to self-renew and differentiate both in *in vitro* and *in vivo* while restraining concerns regarding immune response and ethical and legal administration [4].

MSC can be isolated from a wide range of foetal and adult tissues including bone marrow, placenta, umbilical cord, dental pulp, tendons adipose and etc. However, MSCs are scarce within tissues so that their use in clinical applications is strictly limited [5]. To date, the shortage of these cells is addressed by expanding MSCs by *in vitro* cell culture systems. Two dimensional (2D) plastic cell cultures have been the preferred methods for decades as relatively simple and highly reproducible. After being isolated, cells are seeded on flat surfaces and easily controlled, analysed and manipulated. However, 2D cultures induce MSCs to lose their stemness and indeed their therapeutic potential in restoring tissues and organs. Structurally, 2D cultures fail to resemble the composition and structure of the native microenvironment or niche onto which MSCs reside [6]. The niche are specialised microenvironments that regulate stem cell fate by providing essential cues in the form of cells, ECM and soluble factors [7]. Recently, these niche-based features have been recapitulated by 3D cultures which have conferred a high degree of clinical and biological relevance to *in vitro* models. Especially, those derived from MSCs offer the potential to recapitulate some of the complex aspects of tissue development and homeostasis while addressing fundamental questions about diseases and their progress. In traditional 2D monolayer culture, MSCs often decrease their replicative ability and differentiation potentials as the passage number increased. In contrast, 3D cultures encourage MSCs to behave morphologically and functionally different.3D techniques built on fundamentals of cell-cell and cell-matrix interactions whereby cells are often embedded in matrices or scaffolds and encouraged to proliferate and polarise according to the organ of origin. Collagen, Chitosan, Polycaprolactone (PLC), Polyethylene Glycol (PEG) are some examples of biomaterials that have greatly contributed to improve our understanding not only on MSC biology, but also to aid in developing new therapies for a large number of critical diseases. However, the current 3D cultures still fail to resemble the complex vascular systems that support tissues for oxygenation, nutrients, and waste removal, leading multi-factorial disorders (e.g. diabetes) to be unsuccessful studied and/or treated *in vivo* [8]. Progress in the study of stem cell technology has enabled the development of multicellular 3D cell cultures such as spheroids and organoids. Although they differ in both features and functions, these techniques employ standard tissue culture set up for the self-renewal and organisation of cells into specific multicellular tissue proxies. Once encapsulated within a biomaterial and/or in presence of suitable external cues, MSCs have shown capabilities to form anatomical structures made by clusters of functionalised cells that displayed native phenotypic and morphological signatures [9]. Within organoids, in particular, the anti-inflammatory and angiogenesis properties as well as stemness and differentiation of MSCs have been found to be extremely enhanced after transplantation. Compared with spheroids, organoids are constructed from adult or pluripotent stem cells and yield systems that reflect the genomic makeup of a patient [10]. For instance, Ishida *et al.*, by creating conditions that resembling intestinal injury, reprogrammed MSCs which in turn promoted the growth of colon organoids [11]. Moreover, combination of MSCs with epithelia and tooth germ led the development of new teeth which displayed normal structures and neuro-activities [12]. This is an obvious advantage as organoids provide stable systems amenable to extended cultivation and manipulation

of MSCs while being more representative of *in vivo* physiology [13]. Given that, there are still key limitations that continue to conceal their clinical translation including their reproducibility, scalability and safety profile. It is believed that the introduction of more complex structures including vascular and immune systems and the presence of a defined microenvironment capable to regulate the spatiotemporal control of cell activities could lead this endeavour soon a reality. Organoid systems have already proven themselves to be a great tool for regenerative medicine, and their recent combination with innovative platforms such as nanomaterials has offered unmatched possibilities for creating complex and functional organs that more faithfully recapitulate the *in vivo* situation [14].Therefore, the combined emergence of these new technologies raise hopes for the development of novel methods capable to meet the necessary MSC numbers required for organ transplantation and the time and cost limitations associated to their *in vitro* manipulation.

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