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Introduction to Series on Mesenchymal Stromal (Stem) Cells—MSCs

Timothy O'Brien and Frank Barry

THROUGH INITIAL WORK by Friedenstein *et al.*¹ a stem cell population with the potential to differentiate into cells of a mesenchymal lineage was described. This cell predominantly resides in the bone marrow compartment, but has more recently been described in other tissues.^{2–4} This cell population is termed a “mesenchymal stromal cell”, or MSC. These cells are generally identified through a combination of poorly defined physical, phenotypic, and functional properties, and do not express typical hematopoietic lineage markers.⁵ Biologic and clinical interest in MSC has increased dramatically over the last two decades, as evidenced by the increasing number of research teams investigating these cells.⁶ The International Society for Cellular Therapy (ISCT) has published a consensus document which set about standardizing the definition of the MSC.⁷ This cell population exhibits the following quite nonspecific features—plastic adherence in culture conditions, expression of surface markers such as CD73, CD90, and CD105, and the ability to differentiate into osteoblasts, adipocytes, chondroblasts, and other cell types under certain culture conditions.⁷

MSCs have been utilized now in a large number of clinical trials and the time is opportune to present an overview series of review articles as the one planned for the coming issues of *Human Gene Therapy*. While the mechanism of the therapeutic action of MSCs is not fully understood it is becoming increasingly accepted that the effects are paracrine in nature in many settings. However, in each application it is necessary to consider whether MSCs are having a direct effect via differentiation into host tissue or whether the effect is mediated via the secretion of factors which have beneficial effects on tissue repair and regeneration. An understanding of the mechanism of action may result in the development of novel therapeutic approaches.

The review series will contain articles which focus on the basic and translational science of MSCs. Therapeutic success in the future will be more likely if a solid understanding of MSC biology underpins translational efforts. The first 3 articles in the series will focus on basic aspects of MSC biology. Pierre Charbord provides a historic overview of the MSC and Paolo Bianco reviews the nature of MSCs in this issue.

As the therapeutic potential of these cells in some circumstances will require cell differentiation Cosimo Di Bari will review the regulation of differentiation.

MSCs have therapeutic potential in many disease states but progress to the clinic is most advanced in cardiovascular disease and orthopaedic disorders. Mary Murphy will review the use of MSCs in osteoarthritis and Christoph Stamm will review their use in myocardial infarction.

Another fascinating characteristic of these cells is their immunomodulatory potential. This opens many therapeutics avenues in which this cell type may have therapeutic benefit. Bernard McMahon and Matthew Griffin will present an overview of general immunologic properties while Armand Keating will review the use of MSCs in one specific disorder, GVHD.

There is increasing interest in the interaction between MSCs and cancer. MSCs may be used to target cancer and deliver therapeutic products. In contrast, there is a suggestion that MSCs may have cancer promoting properties either via supporting metastasis or potentially through angiogenesis. Roisin Dwyer and Michael Kerin will review MSCs and cancer.

There is a substantial literature on the use of genetically modified MSCs for therapeutic purposes in preclinical models. Genetic modification of these cells has been achieved by using a wide variety of vector systems which has resulted in enhanced therapeutic efficacy. Gene transfer to MSCs may promote cell survival after engraftment or to enhance the therapeutic paracrine effect. Victor Dzau and colleagues will review progress with genetic modification of MSCs.

The ultimate therapeutic use of MSCs will require efficient protocols for GMP grade cell production. Challenges include efforts to avoid the use of foetal calf serum. Practical aspects of GMP manufacture of MSCs will be reviewed by Luc Sensebe. This will include a discussion of karyotypic abnormalities after cell culture.

In summary, MSCs have been shown by many groups to be beneficial in many disease states. They now offer a new paradigm in medical therapy, with potential to differentiate into tissues such as bone and cartilage or to offer therapeutic

benefit through paracrine mechanisms. To date there is substantial evidence of safety with the use of MSCs although convincing and consistent evidence of benefit is yet to be provided. An understanding of the biology of MSCs may allow more effective therapeutic use of MSCs to be developed. This series will review the basic biology of MSCs and review current progress in the translation of this knowledge to the clinic.

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