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iPSZÜRICH

A Lecture Series Focused on Induced Pluripotent Stem Cells

Ollscoil na Gaillimhe
University of Galway

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MSCs: OBSTACLES TO EFFECTIVE TRANSLATION

Mesenchymal stromal cells have attracted a great deal of attention because of their potential therapeutic use in a broad array of inflammatory and tissue repair applications. Very large numbers of pre-clinical studies have been concluded and some 1500 patient trials are registered. Many of the pre-clinical studies have suggested that both autologous and allogeneic delivery of cells leads to an effective outcome. It has been possible to gain insight into the therapeutic mechanisms underpinning the clinical activity. At this time it is considered that three essential elements contribute to this: (1) the release of paracrine factors which interact with host cells and elicit a repair response, (2) apoptosis of the delivered cells leading to clinical immunosuppression and (3) the release of extracellular vesicles with a cargo of RNA and proteins that exert anti-apoptotic and anti-inflammatory effects on target cells.

In recent years it is apparent from a number of large, well designed and statistically robust clinical trials that an effective therapeutic outcome is not always seen. It appears that achieving a uniform and reproducible outcome in these patient studies is challenging. A significant contributor to this is a low level of consistency in manufacturing protocols and the inclusion of multiple processing variables, including cell source, expansion protocol, media selection and dose. In addition, widely used release criteria for these cell products are of minimal value and fail to reveal phenotypic variations and population heterogeneity. The outcome of this dual hazard is that cells with dramatically different biological phenotype are used in patient trials, contributing to variable clinical outcomes. Several strategies are possible to resolve these difficulties and include the use of induced pluripotent stem cells rather than primary cells as well as forensic attention of processing parameters and the adoption of international standards for testing and release.