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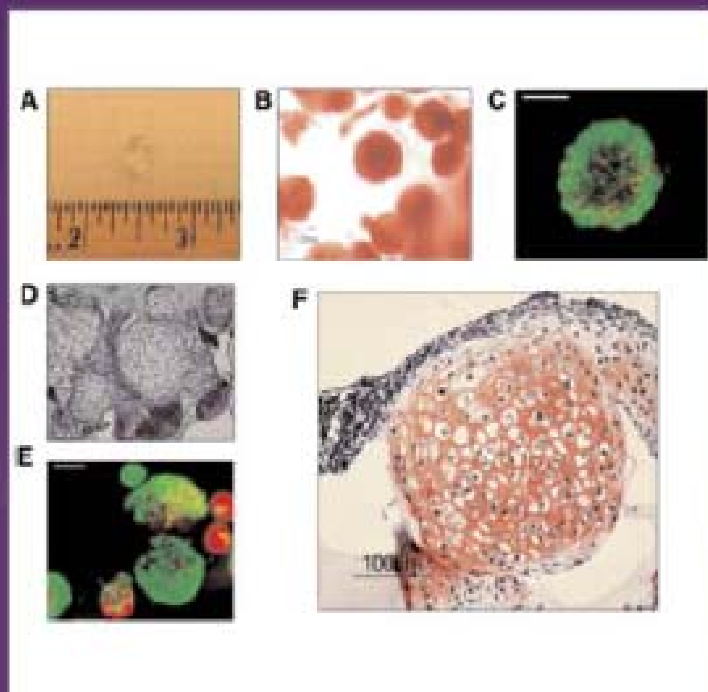

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EMERGING TRENDS IN CELL-BASED THERAPIES

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Preface

Emerging trends in cell-based therapies ☆

Cells are currently used as substitutes of damaged cells (cell replacement therapy), components in reconstruction of regenerated tissues (tissue engineering), and drug delivery vehicles. The use of dendritic cells as cell vaccines is also emerging immuno-therapy. Cell-based therapeutics holds great promise for treating both genetic and acquired diseases, such as cancers, tissue damages and diabetes among others. However, several barriers must be overcome to turn cell-based therapeutics into reality. Immune tolerance, biomimetic materials for tissue engineering and control of stem cell differentiation are formidable tasks to be addressed. On the other hand, genetic modifications of cells for transplantation offer great hope. This theme issue aims at bringing together several key scientists to discuss the emerging trends in cell-based therapeutics. This issue can be divided into three sub-themes: (i) biological views of cell-based therapy, (ii) new biomaterials for cell-based therapeutics, and (iii) integration of cell-based therapy with drug delivery and tissue engineering.

The most common problem in transplantation is the host rejection, which is even more prominent in the case of type 1 diabetes. Thorough understanding of the immune tolerance and our ability to develop various immune tolerogenic cells are the prerequisites for cell-based therapy. Shu-Hsia Chen and associates discuss the major tolerogenic cell populations and their mechanisms of action, with focus on the potential exploitation of their tolerogenic mechanisms for clinical applications. Following this review, a typical application of immunotolerance is presented by Massimo Trucco and associates. In case of type 1 diabetes, insulin producing β cells are destroyed by autoimmune attack. However, restoration of self-tolerance must be reached to recover a cell source capable of functional insulin production. Multiple strategies aimed at modulation of both central and peripheral immunity of type 1 diabetes are discussed. Then, another issue is to search for β cell substitutes in the absence of human pancreas progenitor cells. Therefore, the use of embryonic stem cells and stem/progenitor cells from other tissues for β cell replacement therapy is discussed by Shimon Efrat.

Immunoreaction can be minimized by encapsulation of transplanted cells, which is discussed by John Wison and Elliot Chaikof. Microencapsulation is the widely explored strategy, but full immunoprotection is not yet achieved, possibly due to inadequate transport of nutrients, deleterious innate inflammatory responses, and immune recognition of encapsulated cells via indirect antigen presentation pathways. Current strategies, such as developing conformal coatings of micron and submicron scale on individual cells or cell aggregates and anti-inflammatory and immunomodulatory capabilities, will play important roles in overcoming these limitations.

Ex vivo genetic modification of cells and tissues prior to transplantation is discussed in two reviews with different focuses, one by Thomas Linn and associates on different modifications and the other by Ian Phillips and Yao Liang Tang on different applications. Genetic modification of β cells and stem cells prior to transplantation improves their survival and function. The modified cells can bear a hostile environment from immune rejection, inflammation, hypoxia and apoptosis. The current applications of gene modified stem cells can be found in cardiovascular diseases, diabetes, neurological diseases (including Parkinson's, Alzheimer's and spinal cord injury repair), bone defects, hemophilia, and cancer.

Dendritic cells can be equipped with antigens and thus are considered as cell vaccines to prevent tumor relapse. In other words, dendritic cell-based therapy can be used for fighting against cancer. Therefore, identification of the mechanisms controlling dendritic cell immunogenecity and understanding of the cell dynamics whereby immune responses are orchestrated are reviewed by Alessio Nencioni and associates.

Biomaterials can be used as scaffolds to provide three-dimensional templates and synthetic extracellular matrix environments to mimic certain advantageous characteristics of the natural extracellular matrix for tissue regeneration. Therefore, understanding how microenvironment affects cellular function and tissue morphogenesis is very important in tissue engineering. Peter Ma discusses different strategies to achieve the biomimetic environment of cells, including chemical synthesis to achieve certain compositions or properties similar to those of the extracellular matrix, novel processing technologies to mimic structural features of the extracellular matrix, approaches to emulate interaction between cells and extracellular matrix, and

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delivery strategies to recapitulate a signaling cascade or developmental/would-healing program.

Stem cells are a natural choice for cell therapy due to their pluripotent nature and self-renewal capacity. Creating reserves of undifferentiated stem cells and subsequent differentiation to a lineage of choice is critical for the clinical success of cell-based therapeutics. Identification of appropriate biomaterials as well as growth factors and morphogenetic factors that support cellular attachment, proliferation and lineage specific differentiation is critical for using stem cells for regeneration of tissue constructs. These issues are reviewed by Jennifer Elisseeff and associates as well as Krishnendu Roy and associates.

Two typical examples of tissue engineering, cartilage tissue engineering reviewed by Cindy Chung and Jason Burdick, and regeneration of spinal cord reviewed by Stephanie Willerth and Shelly Sakiyama-Elbert are also presented in this issue. Cartilage lacks regenerative capabilities, and thus it is important to develop a system that promotes the production of cartilage tissue, with the properties similar to native tissue, accelerates the restoration of tissue function, and is clinically translatable. In the case of cord injury, the inhibitory environment and loss of axonal connections after spinal cord injury pose many obstacles to regenerating the lost tissue. A wide range of cell types have been investigated for such uses and the advantages and disadvantages of each cell type are discussed along with the research studying each cell type.

Conventional methods in tissue engineering involving the seeding of cells into biodegradable scaffolds have several intrinsic shortcomings, including inflammatory reactions and fibrous tissue formation caused by scaffold degradation. One novel way to make tissue constructs is called “cell sheet” technology. This method can be applied in high cell-dense tissue engineering and one typical example is myocardial tissue engineering. Teruo Okano and associates have used temperature-responsive culture surfaces and harvested cells as intact sheets. In this strategy, cell-dense thick tissues are constructed by layering these cell sheets. Electrically communicative 3-dimensional (3-D) cardiac constructs can be achieved.

Finally, cells themselves can serve as drug delivery vehicle, for example, erythrocyte based drug delivery, which is discussed by Mauro Magnani and associates. These cells can be easily processed and could accommodate traditional and biologic drugs. Erythrocytes have been evaluated as drug carriers, as they are safe and efficient for treating several diseases.

We would like to express our sincere thanks to all the contributors of this issue of the Advanced Drug Delivery Reviews. We hope that their outstanding contributions provide greater insight into the emerging trends in cell-based therapy. We hope this issue provides stimulation for innovative approaches and further development in this fascinating field.

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