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**Cardiac tissue development for delivery of embryonic stem cell-derived endothelial and cardiac cells in natural matrices.**

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**Public Summary:**

The packaging and delivery of cells for cardiac regeneration has been explored using a variety of biomaterials and delivery methods, but these studies often ignore one or more important design factors critical for rebuilding cardiac tissue. In this article, we explore the combinatorial use of decellularized tissues, moldable hydrogels, patterned cell-seeding, and cell-sheet engineering and find that a combination of these methods is optimal in the recreation of transplantable cardiac-like tissue *in vivo*. Our data shows that an optimal design for generating cardiac tissue would include (1) decellularized matrix seeded with endothelial cells in a gel layered with (2) prealigned cardiac cell-sheets fabricated using our "wrinkled" microchips and thermo-responsive polymer. This article also introduces a novel method of plasma coating for cell-sheet engineering that compares well with electron beam irradiation methods and may be combined with our "wrinkled" surfaces to facilitate the alignment of cardiac cells into sheets.

**Scientific Abstract:**

The packaging and delivery of cells for cardiac regeneration has been explored using a variety of biomaterials and delivery methods, but these studies often ignore one or more important design factors critical for rebuilding cardiac tissue. These include the biomaterial architecture, strength and stiffness, cell alignment, and/or incorporation of multiple cell types. In this article, we explore the combinatorial use of decellularized tissues, moldable hydrogels, patterned cell-seeding, and cell-sheet engineering and find that a combination of these methods is optimal in the recreation of transplantable cardiac-like tissue *in vivo*. We show that decellularized urinary bladder matrix (UBM), that is compliant and suturable, supports the survival of cell cultures but does not allow maintenance of cell-to-cell contacts of transferred cell-sheets (presumably, due to its rough surface). Moreover, the UBM material must be filled with hyaluronan (HA) hydrogels for smoothing rough surfaces and allowing the delivery of greater cell numbers. We additionally incorporated our previously developed "wrinkled" microchip for inducing alignment of cardiac cells with a laser-etched mask for co-seeding patterned "channels" of cells. This article also introduces a novel method of plasma coating for cell-sheet engineering that compares well with electron beam irradiation methods and may be combined with our "wrinkled" surfaces to facilitate the alignment of cardiac cells into sheets. Our data shows that an optimal design for generating cardiac tissue would include (1) decellularized matrix seeded with endothelial cells in a HA layered with (2) prealigned cardiac cell-sheets fabricated using our "wrinkled" microchips and thermo-responsive polymer [poly(N-isopropylacrylamide)] cell sheet transfer system. (c) 2012 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 2012.

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