Annual Report - Slezak Super Center

01/2019

Production and biomechanical characterization of small-diameter engineered blood vessels comprised of biocomposite material with soft coral ultra-long collagen fibers

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Brief Summary:

This research introduces new bio-composites based on unique collagen fibers derived from soft coral with a supporting hydrogel matrix, towards engineered blood vessels. The following results are associated with the specific objectives outlined in the grant proposal:

(3.1). Various small-diameter tube constructs were successfully generated with different dimensions in the range of 3-6 mm diameter to match those of different blood vessels. The collagen fiber orientations were controlled, allowing to direct cell alignment and tailor the mechanical properties of the construct, according to a bio-inspiring approach.

(3.2) A small-diameter cylindrical graft was mechanically characterized by a tubular inflation test, using a special mechanical setup designed and built to this end. The setup allows applying internal pressure levels (0-300 mmHg). The external deformations in the form of diameter change were measured using an optical extensometer. A hyperelastic type response was identified for the experimental hoop stress-strain curves of the tubular grafts. The pressure-stretch curve was found in the range of native human coronary arteries and similar vascular grafts. The graft compliance was calculated as well, and results show very similar values to those of old coronary arteries and Saphenous vein (which is the gold standard nowadays for coronary bypass surgery). Subsequently, a FE model was generated to predict the mechanical behavior of the tubular construct under inflation test. The FE model consisted of a repeated stack of two-layers having different isotropic homogeneous and hyperelastic constitutive models calibrated to match the axial and circumferential behaviors, respectively. Good predictions obtained by the FE model when compared to the tested range of the construct. However, the results did not correlate with a flat sheet (membrane) model of the tube wall made from the same layers in the tubular model. The FE model calibrated directly for the cylindrical construct could not predict well the stress-strain behavior under uniaxial tensile test of the flat cross-plied sheet, representing the graft wall, with the same average volumetric fiber fraction as that of the grafts. This was attributed to various initial stretching levels that were probably present in the circumferential collagen fibers of the cylindrical graft. This led to a more gradual and delayed recruitment of these fibers and hence to limited force resisting of the applied internal pressure. In the tensile tests of the rectangular flat sheets, however, a higher percentage of the fibers were practically recruited to resist the applied tensile forces.

(3.3) The in vitro biological biocompatibility of the new composite collagen material was assessed. Fibroblast cells were cultured on the collagen fibers alone or on collagen-reinforced PEG-based hydrogels. Quantitative metrics including cell growth and cell alignment were developed based on processing the images acquired from confocal microscopy. Cell growth evaluation was validated using the Alamar Blue assay. The cells demonstrated higher growth rates during the first two weeks, followed by lower yet generally positive growth rates for the following two weeks. The cells remained alive and were highly aligned according to the fiber orientation for the entire duration of the experiments (>28 days). Live-cell confocal imaging revealed highly dynamic activity of the cells including division and migration. Cell migration was typically observed along the direction of the collagen fibers. After cell division, the separated daughter cells typically remain aligned or migrated along the fiber direction.

Publications as a result of Shlezak grant:

1. A paper is currently in preparation.

Poster & oral presentations at conferences as a result of Shlezak grant:

1. Sharabi Mirit, Wertheimer Shir, Shelah Ortal, Haj-Ali Rami and Lesman Ayelet. "Bio-composites based on coral collagen fibers for tissue engineering". The Israel Society for Medical and Biological Engineering (ISMBE) - annual conference, February 2018.
2. An invited talk on this project is planned in the ISMBE conference on Feb 2018.