Bioinspired hydroogels for craniofacial muscle regeneration

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Clinical Need

Traumatic and surgical injuries of facial soft tissue that involve underlying skeletal muscle remain one of the greatest challenges to facial reconstruction. Despite the rather well-known capacity of skeletal muscle to repair, regenerate, and remodel following injury, more severe craniofacial injuries, such as those involving the loss of a substantial portion of muscle tissue are not capable of regeneration on their own and are characterized by volumetric muscle loss (VML) injury, resulting in permanent aesthetic and functional deficits of either the injured muscle or the muscle unit (i.e., in the presence of synergists).

Solution

To overcome the limitations associated with muscle repair after surgical resection, we propose to exploit our novel “bioinspired” hyaluronic acid-based hydrogels. Our key innovation is that our HyA-based hydrogels embody material features for robust muscle regeneration, in which our preclinical findings in biologically relevant rodent models of VML injury demonstrated robust functional recovery, accompanied by volume reconstitution, muscle regeneration and native-like vascularization.

Competitive Advantage

To address limitations with current treatment options for VML, we developed a highly tunable hydrogel that allows independent control over the following hydrogel properties, including: (1) the density of peptide sequences for cell attachment via cell-surface integrins; (2) matrix modulus; (3) the cell-mediated degradation kinetics by selective MMPs; and, (4) sequestration of exogenously added or endogenously synthesized growth factors via heparin conjugated within the hydrogel.1-5 These hydrogels are based on the natural biopolymer hyaluronic acid (HyA) with well-known biocompatibility. Previously the system has been optimized for vascularization,3, 4 which plays a key role in muscle regeneration. No other hydrogel on the market has demonstrated the remarkable VML regeneration we have attained with our biomaterial.1 To accelerate commercialization and clinical development, we have developed a pre-formed, lyophilized scaffold form of our HyA hydrogel that can be implanted as a medical device.

Target Market

The global market for VML comprises many distinct market segments including craniofacial muscle regeneration. There are approximately 300,000 craniofacial muscle reconstruction procedures per year worldwide. Persistent facial muscle defects resulting from cancer resection is common (e.g., 4-5 cases per week at UCSF), and lip cancer is the most common cancer of the head and neck. Therefore, of the potential craniofacial indications, we chose muscle repair after surgical resection as the first indication for our technology. For many types of defects, currently available treatment options either (1) do not replace or restore the muscle, or (2) decrease the size of the muscle by bringing the free ends together. These surgical treatment options have not changed in 30 years. The result in the lip or mouth is a smaller mouth (microstomia) with suboptimal functional and aesthetic consequences.

Regulatory Pathway

To make a convincing case to the CDRH of the FDA that our product is a device, we have settled on a final form of a lyophilized scaffold, as an off the shelf-stable product, which we call Volumatrix™. Our plan is for functional studies in rat masseter and safety in a large animal model. The pre-formed lyophilized HyA-peptide-heparin scaffold has ‘precedent’ devices that should enable us to finalize our IFU and to engage the FDA via the Q-Sub Pre-submission Program. We anticipate being regulated as a Class III device and we are pursuing a ‘premarketing’ or de novo pathway. We are preparing our Q-sub documents with our regulatory Patsy Trisler, JD, RAC, and advice from Mike Jamieson.

Intellectual Property

A composition of matter patent (owned by UC Berkeley - Growth Factor Sequestering and Presenting Hydrogels U.S. Patent 9,827,272) has been issued and is being nationalized in various jurisdictions, and a second patent has been filed (4/2019) jointly between UC Berkeley and the University of Virginia for use of our HyA-based hydrogels and other form factors (i.e., scaffold) for muscle regeneration. We anticipate additional craniofacial clinical field of use continuations or new patent applications based on discoveries from this grant.

Related Publications

Dienes, J., Browne, S., Farjun, B., Amaral Passipieri, J., Mintz, E.L., Killian, G., Healy, K.E. & Christ, G.J. Semisynthetic Hyaluronic Acid-Based Hydrogel Promotes Recovery of the Injured Tibialis Anterior Skeletal Muscle Form and Function. ACS Biomater Sci Eng 7, 1587-1599 (2021). Jha, A.K., Mathur, A., Svedlund, F.L., Ye, J., Yeghiazarians, Y. & Healy, K.E. Molecular weight and concentration of heparin in hyaluronic acid-based matrices modulates growth factor retention kinetics and stem cell fate. Journal of controlled release : official journal of the Controlled Release Society 209, 308-316 (2015). Jha, A.K., Tharp, K.M., Browne, S., Ye, J., Stahl, A., Yeghiazarians, Y. & Healy, K.E. Matrix metalloproteinase-13 mediated degradation of hyaluronic acid-based matrices orchestrates stem cell engraftment through vascular integration. Biomaterials 89, 136-147 (2016). Jha, A.K., Tharp, K.M., Ye, J., Santiago-Ortiz, J.L., Jackson, W.M., Stahl, A., Schaffer, D.V., Yeghiazarians, Y. & Healy, K.E. Enhanced survival and engraftment of transplanted stem cells using growth factor sequestering hydrogels. Biomaterials 47, 1-12 (2015). Tharp, K.M., Jha, A.K., Kraiczy, J., Yesian, A., Karateev, G., Sinisi, R., Dubikovskaya, E.A., Healy, K.E. & Stahl, A. Matrix-Assisted Transplantation of Functional Beige Adipose Tissue. Diabetes 64, 3713-3724 (2015).