Scaffolding the Scaffold: 3D-Printed External Biodegradable Cage Mitigates Contraction during Maturation of Elastic Cartilage Constructs

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INTRODUCTION: Although in previous work we have successfully generated full-scale ear constructs from human auricular chondrocytes (HAuCs) and Human Mesenchymal Stem Cells, the main obstacle for clinical translation of the constructs is the shrinkage and loss of topographic definition that occurs during their in vivo implantation/maturation phase. It is known that tension forces generated by skin and other surrounding tissues contribute to the contraction and loss of topography of a collagen hydrogel. We hypothesize that 3D-printing of an external cage to surround our collagen-chondrocyte hydrogel will allow us to study how shielding our auricular scaffolds from naturally occurring external forces has the potential to reduce contraction and preserve topography, while not interfering with neocartilage formation.

METHODS: HAuCs were isolated from discarded otoplasty specimens and then encapsulated into 8mm disc type I collagen hydrogels with a cell density of 25 million cells/mL. Custom external cages were 3D-printed out of biocompatible polylactic acid (PLA) with high fidelity contour matching to the hydrogel. The hydrogels surrounded by the PLA cages were implanted into the dorsum of nude mice and explanted after 1 month in vivo for analysis.

RESULTS: The external PLA cages were able to maintain their shape/strength after 1 month in vivo, providing the protection the hydrogels needed for undisturbed formation of neocartilage. After 1 month in vivo, the discs developed a shiny white cartilage-like appearance, similar to native auricular cartilage. The discs maintained in the external cages contracted on average only 4.17%, which is significantly less contraction than our usual human auricular cartilage constructs, which contract at least 25%. In addition, safranin-o staining shows cartilage formation, proving our design allows sufficient flow of nutrients in vivo for chondrocyte survival and function.

CONCLUSION: We have shown that a custom 3D-printed external cage made out of a biocompatible and biodegradable material can be used to mitigate contraction of our auricular chondrocyte scaffolds. We have validated a methodology that not only has the potential to optimize our tissue engineered auricles, but to solve a problem of cartilage contraction well documented in literature that no one has been able to conquer before. The same technique can be applied to create cages that faithfully conform to the contour of full scale auricular scaffolds in order to preserve their complex topography.

CRANIOMAXILLOFACIAL/HEAD & NECK SESSION 3

Implantable Deferoxamine Facilitates Non-Vascularized Grafting in Irradiated Bone

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INTRODUCTION: The goal of this proposal is to therapeutically reverse the damaging effects of radiotherapy on bone formation and healing to enable non-vascularized grafting in irradiated bone. Utilizing a rodent model of mandibular bone grafting, we quantified metrics of diminished graft take and bone healing in response to radiation treatment. Subsequently, we utilized implantable deferoxamine (DFO)-an angiogenic stimulant, to reverse these radiation-induced detriments. We hypothesized that the addition of our proposed therapy, would evidence quantifiable degrees of remediation on the process of tissue regeneration, graft incorporation and bone healing.

METHODS: Male Lewis rats received a human equivalent dose of radiotherapy (7Gy/d x 5d) to left hemi-mandibles. After recovery, a circular trephine burr (6mm) was utilized to create a critical size defect just posterior to the third molar, and a bone graft was harvested from the right hemi-mandible of the same animal and secured with a custom PLA resorbable plate. Three groups (n=8/group) of animals were investigated: Control, (irradiated) XRT and irradiated + implantable deferoxamine (DFO). Mandibles were imaged at 14, 40 and 60 days with in vivo µCT, and a 60-day healing period was allowed prior to further outcomes testing. Bony union was judged clinically by 3 blinded reviewers on a scale from 0 to 4, representing the approximate percentage of robust union formation along the circular graft-recipient site interface (e.g. 1=25%, 4=100%). Statistical comparisons were conducted with ANOVA (p<0.05).

RESULTS: We observed a significant diminution of bone graft healing after radiotherapy. At 60 days, the bone volume fraction (BVF) of the XRT group decreased by 20% (p=0.025), and exhibited lower bony union scores when compared to control (p=0.005). With the addition of DFO, these findings were largely remediated. At 60 days, the BVF improved upon the XRT BVF by 12% (p=0.025), and was not different than control (p=0.282). In addition, the bony union scores of the implanted DFO group significantly improved from XRT levels (p=0.05), and were not different than control (p=0.200).

CONCLUSION: Implantable DFO strongly remediates the effects of radiation on non-vascularized bone graft incorporation and healing as measured by micro-densitometry and bony union analysis. These observations are promising with regards to the potential utility of this therapy to enhance bone graft incorporation in the irradiated mandible for head and neck cancer survivors.