Clinically Translated, Thermoplastic Biomaterial as Absorbable Scaffold for Functional Regeneration of Vascular, Dermal and Other Tissues: Biocoacervation of Purified Extracellular Matrix (ECM) Protein and Glycosaminoglycan

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Statement of Purpose: A breakthrough absorbable material was created and tested in vascular and tissue filler replacement/regeneration applications, including validated manufacturing and demonstrated safety/efficacy in FDA-approved pivitol clinical trial. This ECM-mimetic material technology, which was awarded a 2012 U.S. patent, has thermoplastic ability to be molded into unlimited geometries and coatings down to micron thickness (Masters, D. B., USPTO Patent# 8,153,591). The inventive discovery includes using both a compositional ratio of purified ECM elements and the conditions within which they solubilize and self-assemble via coacervation into a homogeneous, amorphous, non-fibrous, aqueous hydrogel. In additon to its tissue and blood biocompatibility, this novel material is reproducibly manufactured in kilogram scale quantites created de-novo without pre-existing tissue remnants or contaminants, substantiantly overcoming many shortcomings found in degradable polymers and decellularized cadaveric tissue.

Methods: The thermoplastic biomaterial, which is self-assembled from solubilized ECM components, was termed a "Biocoacervate". In general, bovine collagen was dissolved in aqueous solution. Bovine elastin and porcine heparin were dissolved together in another aqueous solution. The collagen and elastin-heparin solutions were brought together, immediately producing an aggregated precipitate and amorphous coacervate that falls out of solution to a form a large cohesive mass. The yields are ~80% based on recovered unused solids (~23% solids and ~77% moisture, based on dehydration assay). The biocoacervate was melted and gently mixed, resulting in a uniform, rubbery, water-insoluble hydrogel at room temperature. This sterilizable, curable, thermoplastic biomaterial was used in coating and fabrication processes, making injectable particulate or formed device constructs for tissue augmentation and repair, including dermal filler and vascular graft applications. Its biocompataility and physico-chemical characteristics were measured, including histology, and mechanical strength measurements.

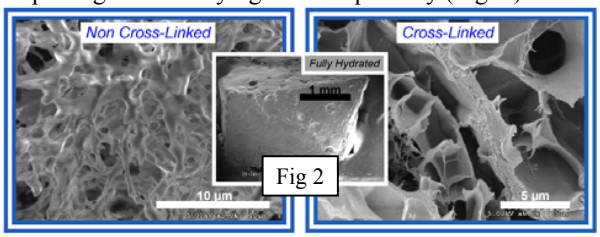
Results: Rheological Testing

The thermoplastic biomaterial was tested mechanically by pressing a 2 mm round probe 4 mm into surface of gel-filled container (1 cm diameter and 1 cm deep as a modified Bloom Test). Fig 1 results show non-crosslinked material is stronger and much more elastic than gelatin.

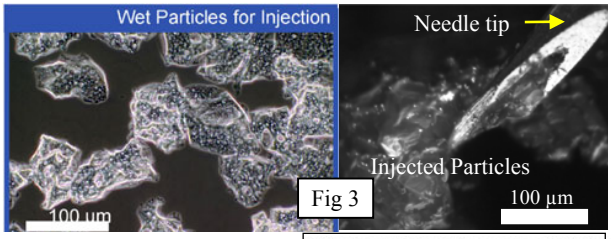
Non-crosslinked Material	Tensile Strength (kPa)	Maximum Load (N)	Young's Modulus (kPa)
Thermoplastic Biomaterial	6.05	4.27	23.93
20.1% Gelatin	4.11	2.90	13.76
13.4% Gelatin	2.00	1.41	7.28
6.7% Gelatin	1.04	0.74	6.54

Fig. 1 chart of rheological data comparing gelatin to thermoplastic biomaterial.

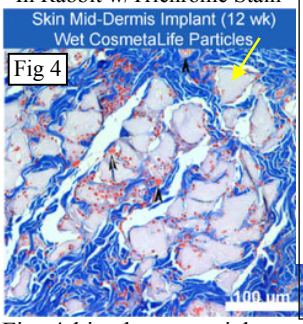
SEM: Thermoplastic Biomaterial w/wo cross-linking and scope-stage freeze-drying to show porosity (Fig. 2).

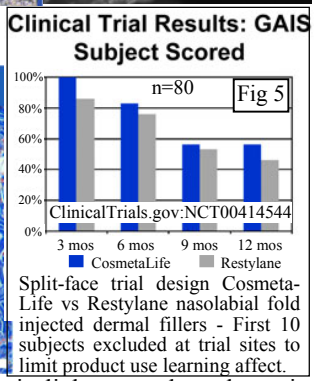


Particles: Thermoplastic biomaterial for injection-dermal filler applications, called CosmetaLife® (Fig. 3).



Tissue Augmentation:
In Rabbit w/Trichrome Stain

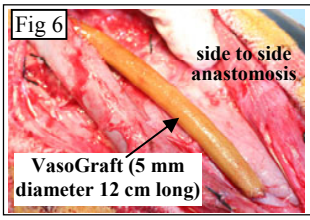




Split-face trial design CosmetaLife vs Restylane nasolabial fold injected dermal fillers - First 10 subjects excluded at trial sites to limit product use learning affect.

Fig. 4 histology, particles stain light grey, dermal matrix dark blue & cells red, (arrow heads depict microvessels). Fig 5 graph of Clinical Trial, FDA-approved double blind, multicenter, ~150 subjects, met primary endpoint for both safety/efficacy. CosmetaLife (blue) outmatched Restylane control in nasolabial fold contralateral correction comparisons in Global Aesthetic Improvement Scale (GAIS).

Vascular Grafts – Preclinical Porcine/Ovine Studies:



Tubes made with thermoplastic biomaterial, called VasoGraft®, tested against ePTFE grafts to shunt carotid artery to jugular vein in two week study (n=6 for each group), show greater tissue integration, less clotting and less thrombogenicity (Fig. 6).

Conclusions: As this scaffolding imparts chemical-structural feedback for natural cell-mediated remodeling, it also precludes blood clotting to allow vessel grafts to carry blood and regenerate/integrate endogenous tissues. By limiting inflammation it provides a temporary cellular support needed to build regenerated, functional tissue.

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