

3-D bioPen: A hydrogel injection to regenerate cartilage

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Development of BioPen. Credit: *Biofabrication*, doi: <https://doi.org/10.1088/1758-5090/aad8d>

Highly specialized cartilage is characteristically avascular and non-neural in composition with low cell numbers in an aliphatic environment. Despite its [apparent simplicity](#), bioengineering regenerative hyaline cartilage in a form effective for implantation remains challenging in musculoskeletal tissue engineering. Existing surgical techniques

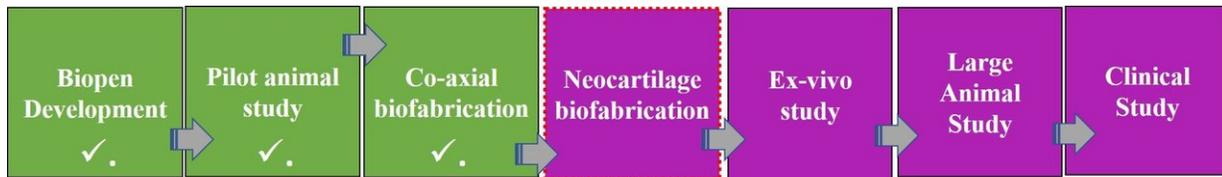
including autologous chondrocyte implantation (ACI) and matrix-induced autologous chondrocyte implantation (MACI) are considered superior to [self-repair induction techniques](#). However, both MACI and ACI are complex, multistage procedures that require a double operation; first for surgical excision of native cartilage, followed by expansion of adult chondrocytes in vitro prior to implantation by a second operation.

Regenerating robust articular hyaline-like [cartilage](#) is a key priority in musculoskeletal tissue engineering to prevent cost-intensive degenerative osteoarthritis that limits the quality of life in global healthcare.

Integrating [mesenchymal stem cells and 3-D printing technologies](#) has shown significant promise in [bone tissue engineering](#)– although the key challenge remains in transferring the bench-based technology to the operating room for real-time applications. To tackle this, [a team of Australian orthopedic surgeons and bioengineers](#) collaboratively proposed an in situ additive manufacturing technique for effective cartilage regeneration. The handheld engineered extrusion device known as the BioPen offers an advanced, co-axial extrusion strategy to deposit cells embedded in a hydrogel material within a surgical setting. The dynamics of material distribution to facilitate cell survival, and the maintenance of mechanical properties for cartilage tissue engineering of BioPen are now published in *Biofabrication*, IOP Science.

In the recent study, Claudia Di Bella and co-workers conducted neocartilage biofabrication as a requisite step in the path toward clinical translation of the BioPen device, preceded by an in vivo proof-of-principle pilot animal study performed in a sheep model. The authors used human adipose-derived [mesenchymal stem cells](#) (hADSCs) laden in gelatin methacrylate (GelMa) and hyaluronic acid methacrylate (HAMa) hydrogels, extruded via the BioPen to generate bioscaffolds that formed hyaline-like cartilage. The authors replicated the previously established protocol to [synthesize the GelMa/HAMa](#) hydrogel. The surgical device showed capacity to biofabricate a regenerative stem cell niche in situ

with future potential to change the existing clinical approaches in surgical practice for organ and tissue regeneration.



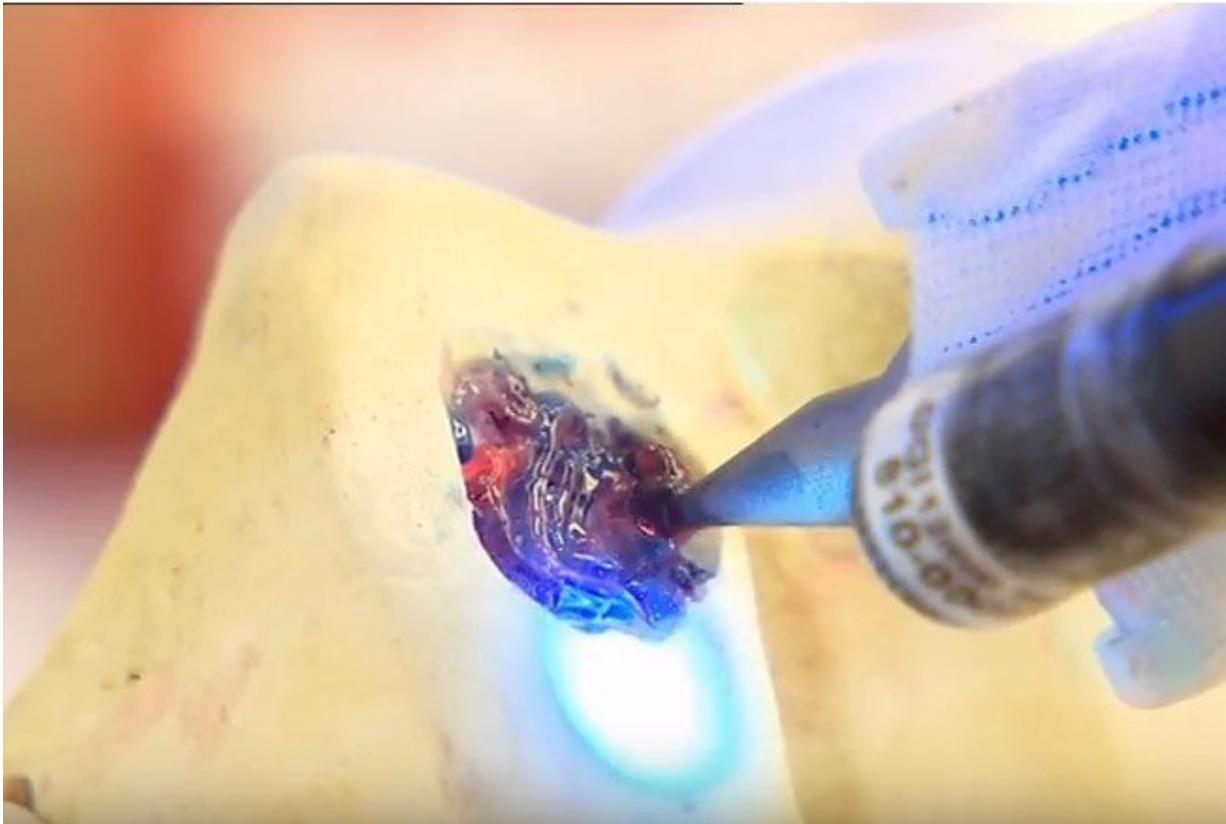
The bench to clinic framework of materials development for clinical translation of the BioPen device. The flow chart lists the steps achieved (green) and the steps projected (purple). The present stage is neocartilage biofabrication (red highlight), this is the final step for in vitro analysis, prior to ex vivo and in vivo animal studies. Credit: Adapted from *Biofabrication*, doi: 10.1088/1758-5090/aad8d

Human stem cells were harvested from the infrapatellar fat pad (IPFP) of patients undergoing total knee replacement. To control the size and shape of the scaffolds extruded by the BioPen, the authors used polydimethylsiloxane (PDMS) cylindrical molds to create a desired shape with regulated cell numbers, providing reproducible structural organization with 3-D geometry for mechanical testing. Immediately after extrusion, samples were irradiated with UV light for photopolymerization. Materials were characterized with mechanical loading tests for compression and atomic force microscopy (AFM) to determine surface topology.

The capacity to produce hyaline-like neocartilage was analyzed using the cellular response to the chondrogenic stimuli via histology, gene and protein expression analysis. The building of new tissue was defined by protein localization and organization of the main components of hyaline

cartilage. The neocartilage function was determined via mechanical properties with time.

The study demonstrated the capacity of the BioPen to produce human hyaline-like cartilage by coaxial extrusion of hADSC-laden in GelMa/HAMa hydrogel. A handheld device for surgical extrusion can also overcome clinical graft-site mismatch limitations. The [previously established core/shell distribution](#) of the scaffold geometry protected the survival and proliferative potential of the hADSCs. Genes expressed during hyaline-like cartilage formation were quantified with qRT-PCR, the expression of [SOX9](#) – the master regulator of chondrogenesis reflected the chondrogenic potential of the [stem cells](#) source. Cells similarly expressed [COL2A1](#) (type II collagen found in cartilage) and [ACAN](#) (that forms proteoglycan protein) to demonstrate differentiation. Bioscaffolds were further tested using non-linear two-photon microscopy and second-harmonic generation (SHG) to detect mature fibrillary collagen after eight weeks of chondrogenesis.



Extruding gel with UV light for photopolymerization. Credit: Melbourne Medical School, *Biofabrication*, doi: 10.1088/1758-5090/aad8d

The possibility of delivering osteogenic and chondrogenic growth factors within the hydrogel will be considered in the future. Additional studies will also aim to achieve biomechanical properties for the chondrogenic bioscaffolds comparable to native articular cartilage. Studies hereon will evaluate de novo cartilage formation to understand [the interplay between stem cells and 3-D architected hydrogels](#) with different mechanical and biodegradation properties.

More information: Carmine Onofrillo et al. Biofabrication of human articular cartilage: a path towards the development of a clinical

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