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"*Silk fibroin modulates the mechanical properties of alginate-gelatin hydrogels and controls cardiac cell contractile function in cardiac bioinks*"

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Cardiovascular disease, which includes heart attacks and heart failure (HF), is the leading cause of mortality globally. Despite its risks and limitations, heart transplantation remains the primary treatment for HF. To tackle the donor heart shortage and enhance treatment outcomes, innovative approaches such as stem cell therapy and tissue engineering have been explored to develop functional cardiac tissues.

Previously, we created cardiac bioinks incorporating cardiac spheroids and hydrogels composed of alginate (Alg) and gelatin (Gel), demonstrating promising effects on cardiac tissue engineering and regeneration both *in vitro* and *in vivo*. Silk fibroin (SF), a natural protein derived from *Bombyx mori* silkworm threads, has emerged as a potential biomaterial for cardiac bioink formulations due to its adjustable properties and minimal immunogenic response. Nevertheless, SF solutions require modifications for effective printing as a standalone component.

This study is the first to investigate the impact of incorporating SF into Alg-Gel hydrogels on cardiac cell viability *in vitro* and cardiac function *in vivo*. Initially, we characterized the structural and elastic properties of the SF-Alg-Gel hydrogels. Subsequently, we assessed their printability and durability, along with their influence on the viability and contractile activity of cardiac spheroids. Finally, we examined the effects of SF-Alg-Gel hydrogels on cardiac function using an *in vivo* myocardial infarction mouse model.

Our results indicated that adding 1% (w/v) SF to Alg-Gel hydrogels enhanced their elastic properties without compromising cell viability. Moreover, cardiac spheroids embedded in Alg-Gel hydrogels containing 1% (w/v) SF exhibited a double increase in fractional shortening (FS%), indicative of improved contractile activity [1]. Additionally, the application of cardiac patches made from 1% SF-Alg-Gel hydrogels improved the left ventricular ejection fraction (LVEF%) by 20% in infarcted mice.

In summary, our findings represent a significant advancement in the biofabrication of advanced cardiac tissues for tissue engineering and regenerative medicine. Further long-term in vitro testing and large animal studies are essential before progressing to potential clinical trials in humans (Figure 1).

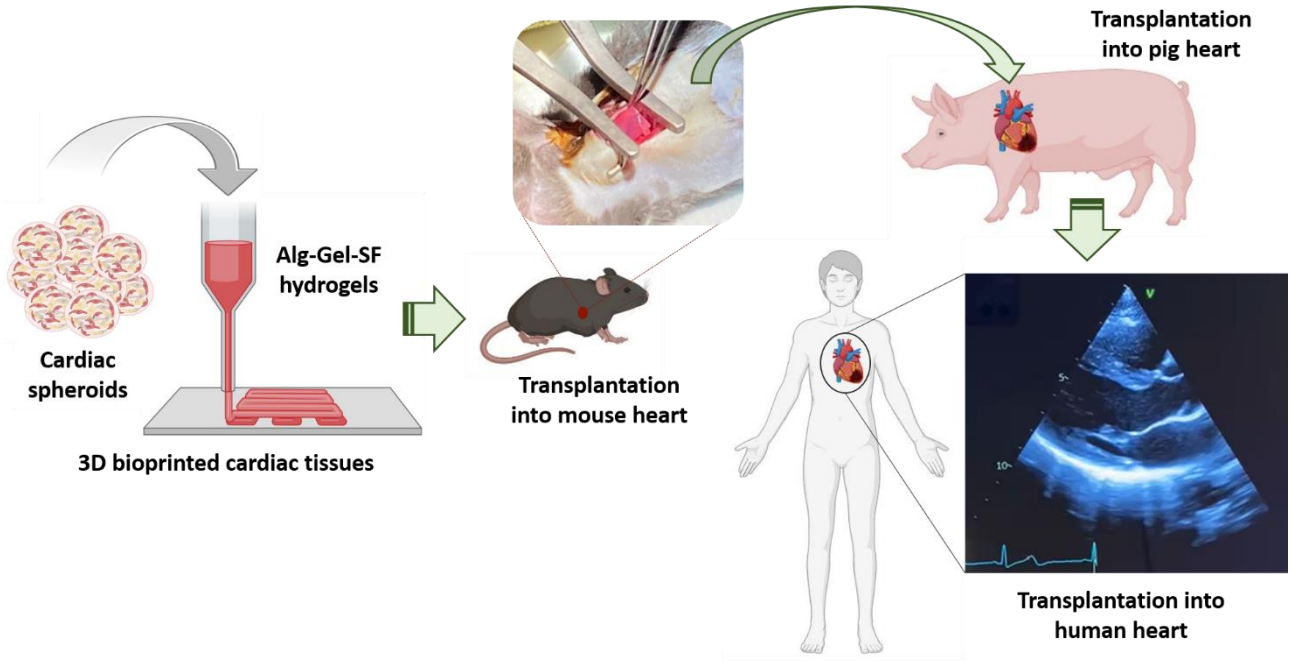

Figure 1. 3D bioprinting of cardiac tissues and *in vivo* transplantation.
Schematic representation of cardiac bioink preparation to 3D bioprint and mimic cardiac tissues. The 3D bioprinted cardiac tissues will be transplanted into an MI mouse model and then into a bigger MI model such as pigs, followed by humans (Alg=alginate, Gel=gelatin, SF=silk fibroin). Figure by the author, using BioRender.

Keywords: silk fibroin, bioink, cardiac spheroids, *in vivo* study.

References

[1] *Silk fibroin increases the elasticity of alginate-gelatin hydrogels and regulates cardiac cell contractile function in cardiac bioinks*. Vettori L., Tran A. H., Mahmodi H., Filipe E. C., Liu Chung Ming C., Cox T. R., Tipper J., Kabakova I. V., Rnjak-Kovacina J. and Gentile C., **Biofabrication**, **16**, 2024 (https://iopscience.iop.org/article/10.1088/1758-5090/ad4f1b)

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