Joining forces: combining stem-cell derived nanovesicles and biomaterials for cardiac repair

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Cardiovascular diseases are the leading cause of mortality globally, yet current treatments fall short in their capacity to repair and regenerate the heart. Novel therapies are imperative and should address various mechanisms of cardiac repair concurrently (i.e., pro-angiogenic, anti-fibrotic and pro-survival). Extracellular vesicles (EVs) have emerged as important mediators of stem cell-induced cardiac repair due to their ability to package and deliver their multifaceted cargo (i.e proteins, lipids, miRNA) to influence target cell behavior[1]. However, clinical utility of EVs has been hindered by their low production yield and rapid clearance in the body[2]. Recently, our team developed a rapid, size-based extrusion strategy to generate EV-like nanovesicles (NVs) from human stem cells in large quantities with cardiac reparative function.[3] Here, we hypothesise that combining NVs with photo-crosslinked silk hydrogels will provide sustained and localised delivery of reparative signals while creating an ideal environment for tissue regeneration. We demonstrate that NVs can be encapsulated within silk hydrogels, released over an extended period of time and remodel recipient cells proteome towards neovascularization, ECM regulation, and tissue repair *in vitro.* This work represents a significant stride in advancing EVs as viable therapeutic option.

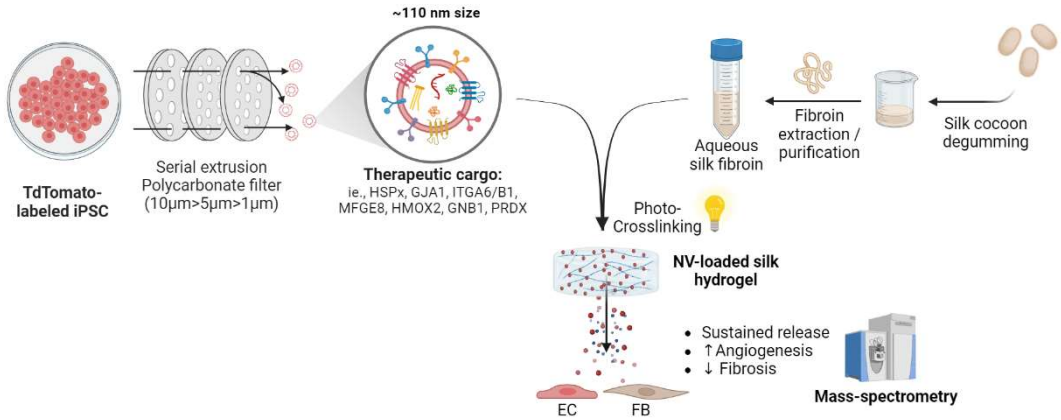

Figure 1. Graphical abstract: Large scale generation of stem cell-derived nanovesicles containing multi-modal therapeutic cargo and encapsulation within silk fibroin hydrogel by photo-crosslinking for sustained release. Abbreviations: HSPx: Heat shock proteins family; GJA1: Gap Junction Protein Alpha 1; ITGA6/B1: integrin subunit alpha 6/beta 1; MFGE8: milk-fat globule-epidermal growth factor 8; HMOX2: Heme oxygenase 2; G protein subunit beta 1; PRXD: Peroxiredoxins family; iPSC: induced pluripotent stem cell; EC: endothelial cells; FB: fibroblasts; NV: nanovesicles

References:

[1] Rai, A., *et al*. *Journal of Extracellular Vesicles* **10**, e12164 (**2021**).
[2] Claridge, B., *et al*. *Frontiers in Cell and Developmental Biology*, 2307 (**2021**).
[3] Lozano, J. *et al.* *International Journal of Molecular Sciences* **23**, 14334 (**2022**).