A Replenishable Cell Delivery System for the Heart

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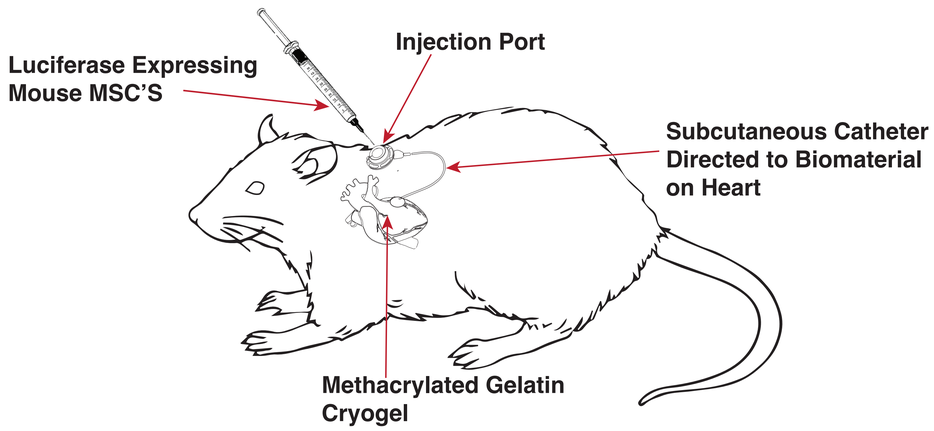
Introduction

• Coronary artery revascularization therapies are effective at restoring blood flow to the heart following an infarct, however residual myocardial scarring remains permanently. Elimination of myocardial scarring and restoration of full cardiac function post-MI could eliminate the cascade of events that lead to heart failure.

• At present there is a total absence of effective therapies in this domain. Cell delivery to the infarcted heart is an exciting and promising therapy, but poor cell survival and retention necessitates multiple, invasive administrations of cells.

• In the present study we developed an approach to enable non-invasive multiple replenishments of biological therapy to the heart, and demonstrate its function in a pre-clinical rodent model.



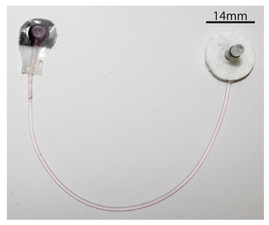
Materials and methods

Cell Delivery
A methacrylated gelatin cryogel seeded with 1 million luciferase expressing mouse mesenchymal stem cells (D1,balb c), was sutured to the epicardial surface of the rat heart. An implantable catheter was used as a conduit between this reservoir and a subcutaneous port located between the shoulder blades of the rat. The biomaterial reservoir could be refilled with cells (1 million cells/50 μl) through the port at defined time points.

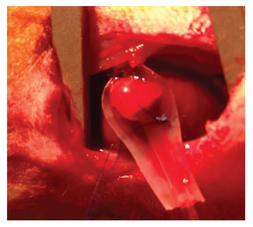
Small Molecule Delivery
A targeted injection of D-Luciferin (0.75mg/50μl) was delivered to the biomaterial reservoir through the injection port. The subsequent bioluminescence produced by the luciferase expressing cells was used as a measure of cell viability.

Protein Delivery
Targeted protein delivery to the biomaterial reservoir and sustained release at the epicardial surface of the heart was demonstrated via administration of fluorescent bovine serum albumin (0.3mg/100μl) through the injection port.

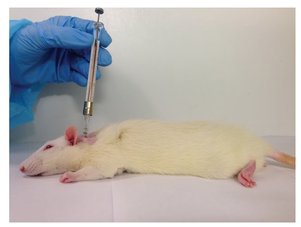
Delivery System



In-Vivo Attachment

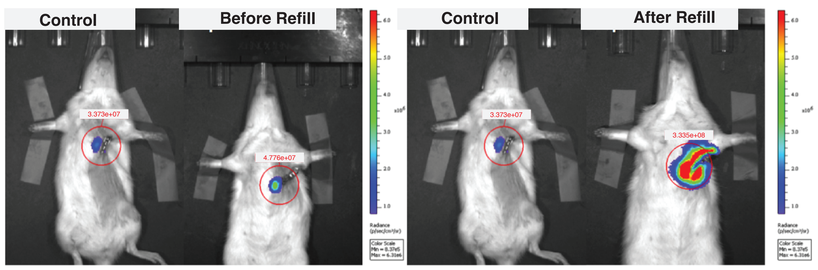


In-Vivo Refill

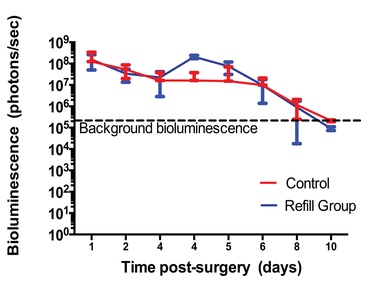


Results

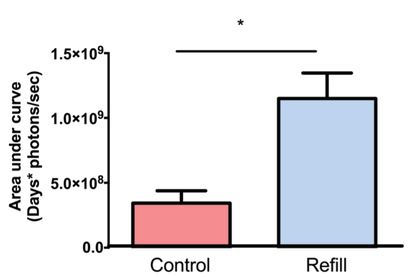
Cell delivery



(A) A representative bioluminescence image and quantification of the control (non-refill) and experimental (refill) group

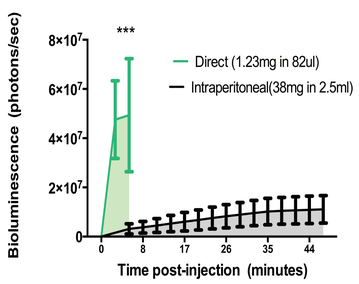


(B) Bioluminescence for control (non refill) and refill group from day 1 (day of surgery) to day 10. Data are mean ± SD (n=5).



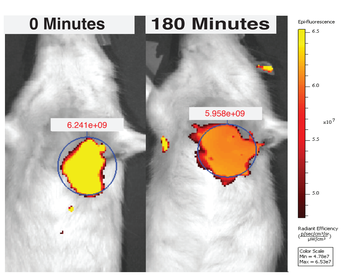
(C) A comparison of the area under the curve for the control (non refill) and refill group. Data are mean ± SD. *p<0.05 by T-test.

Small molecule delivery



(D) Bioluminescence for direct and intraperitoneal delivery of imaging substrate D-Luciferin, data are mean ± SD.

Protein delivery



(E) Direct injection of fluorescent bovine serum albumin (0.3mg/100 μl)

Conclusion

• The biomaterial reservoir could be refilled with cells through the injection port increasing the resident cell number 10-fold (graph A,B,C).

• This delivery system applies dosage form design to cell therapy, and will simplify cell dosage analysis for the treatment of cardiac disease.

• The system also allows targeted injection of molecular therapies directly to the epicardial surface of the heart (graph D,E).

• We present a delivery system that allows targeted, replenishable and sustained presentation of cellular therapy to the heart. This system provides a platform for other therapeutic strategies (small molecules, proteins) and delivery to other diseased tissues.

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