INNOVATIVE BIOMATERIAL-BASED STRATEGY FOR SYSTEMIC DELIVERY OF HUMAN MESANGIOBLASTS IN AN IMMUNODEFICIENT DMD MOUSE MODEL

AMER S., BRAGG L. , SANTOLERI S., COSSU G. AND GALLI F.

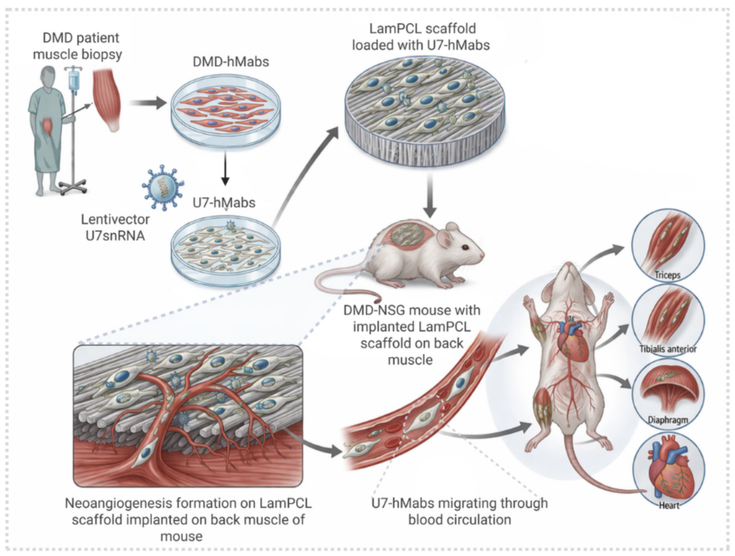
1.Division of Cell Matrix Biology & Regenerative Medicine, Faculty of Biology, Medicine and Health, University of Manchester. Manchester Academic Health Science Centre, M139PL Manchester UK.
2.Department of Veterinary Surgery, Alexandria University, Egypt

Abstract

Delivery of cells or vectors in advanced therapies is probably the major challenge for genetic disorders that affect a large part of the body such as Duchenne Muscular Dystrophy (DMD).

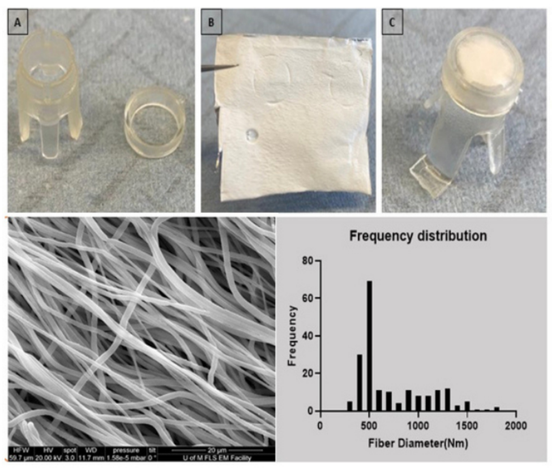
Here, we describe a novel approach for systemic cell delivery based upon an implantable bio-scaffold composed of aligned nanofibers to support adhesion and extensive proliferation of mesoderm cells both in vitro and when implanted subcutaneously in a DMD mouse model.

The scaffold is rapidly vascularised leading to cell entering the circulation and colonising multiple distal organs, including distant skeletal muscles and heart.



Methods

- **NF scaffold fabrication, customisation, and morphological characterisation by SEM.**

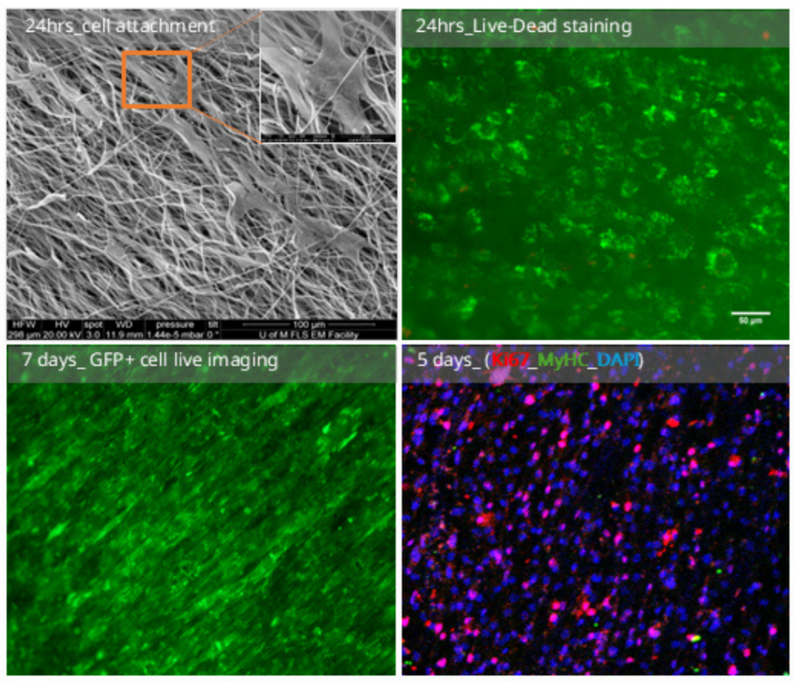


Conclusion

These advances lay the foundation for a transformative cell delivery platform that could eliminate the need for invasive catheter-based systemic administration, not only for DMD but also for other widespread monogenic diseases of the solid mesoderm, including most muscular dystrophies.

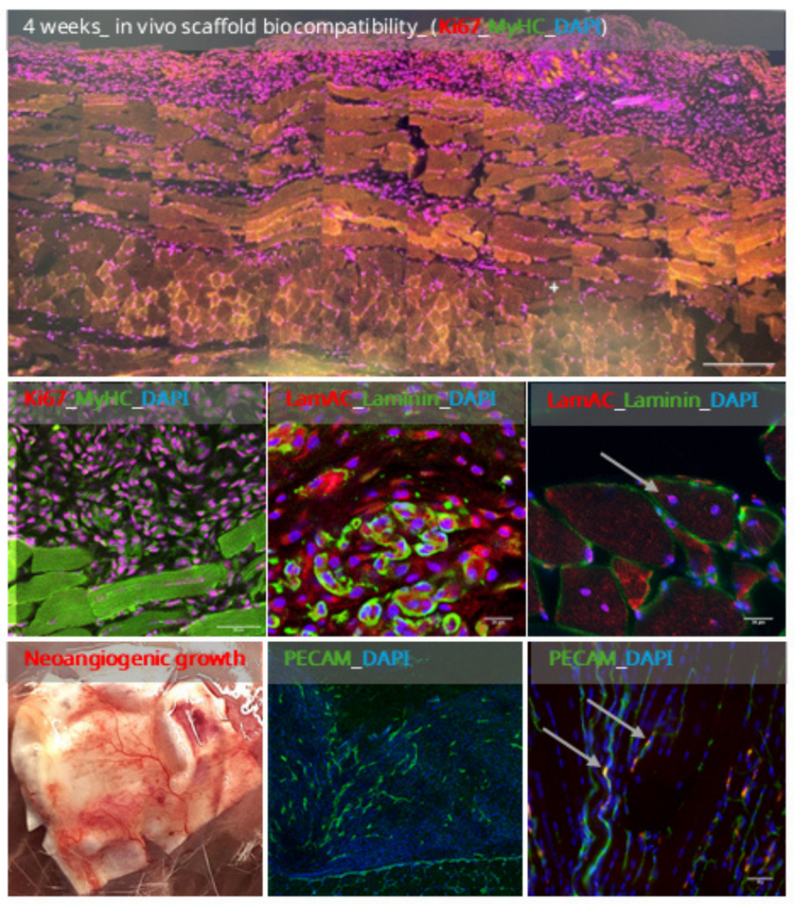
Results

- **NF Scaffold-cell interaction, biocompatibility, and proliferation rate assessment in vitro.**



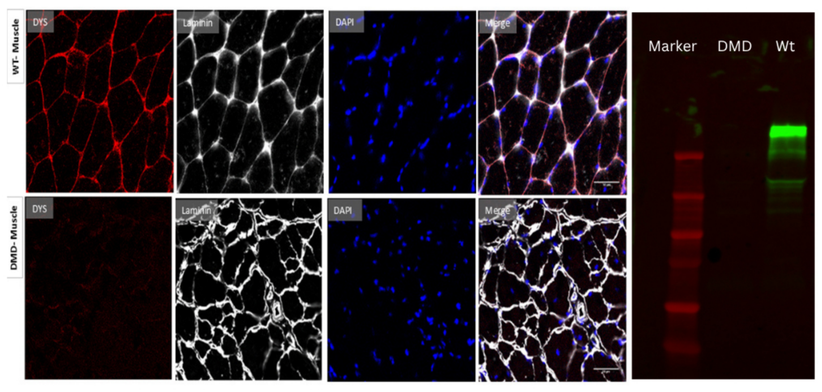
Ki67, cell proliferation marker. **MyHC**, muscle cell differentiation marker

- **overview of in vivo NF scaffold loaede with human mesangioblasts**
- **in vivo scaffold biocompatibility, cell survival, human cell migration and angiogenesis formation.**



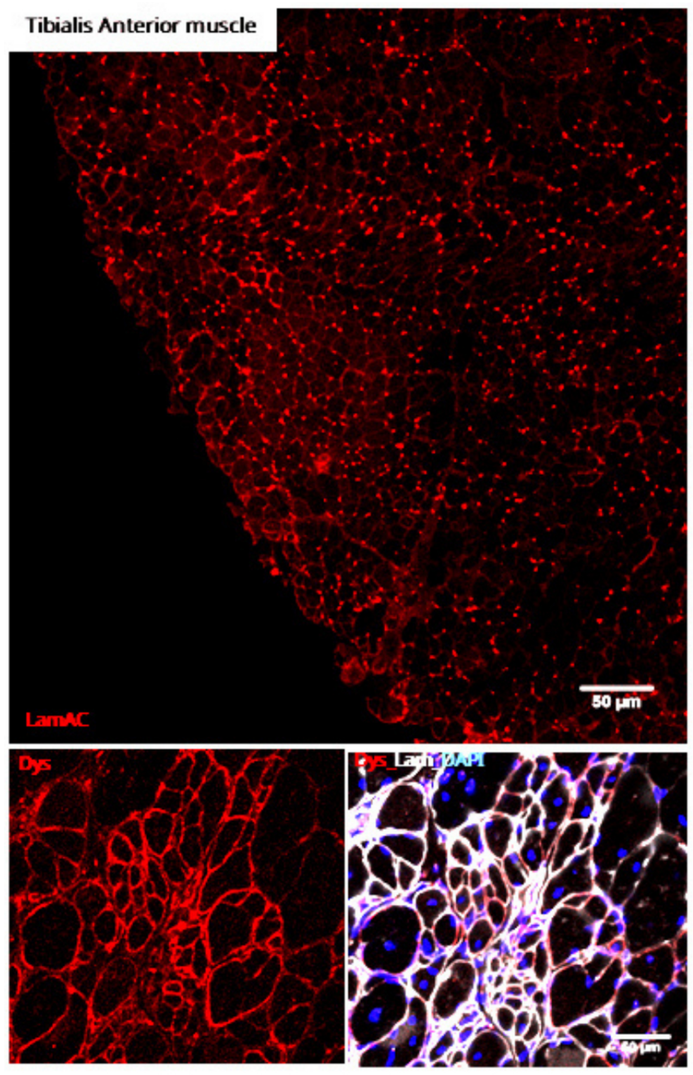
LamAC, human speicifc nuclear antibody. **Laminin**, a basement membrane marker. **PECAM**, endothelial cell marker

- **DMD-NSG animal model characterisation for lack of dystrophin expression.**



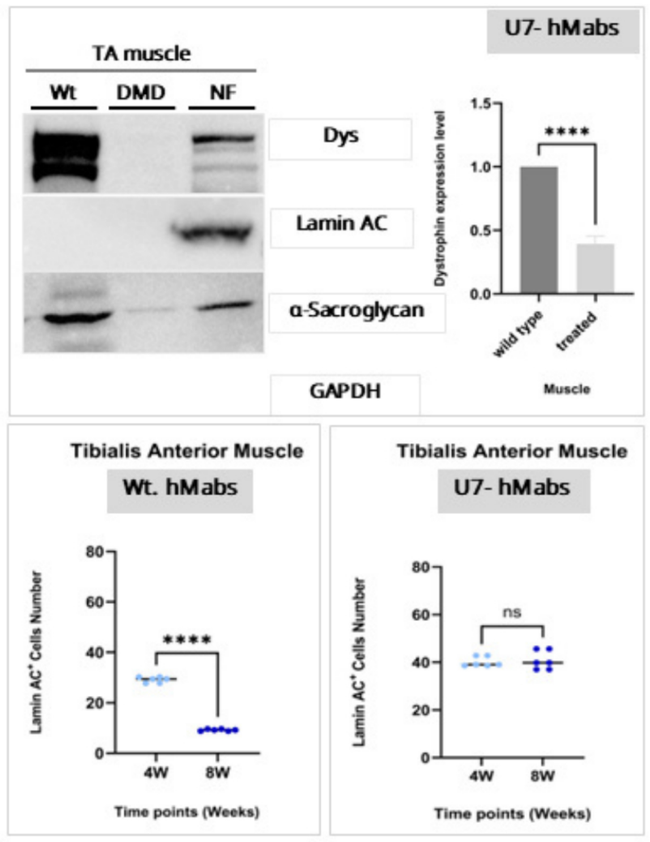
Dys, dystrophin protein marker. **DMD**, Duchenne muscular dystrophy. **Wt,** normal muscle as a control.

- **Assessment of human mesangioblast migration, and dsytrophin restoration in DMD animal model**



- overview of TA muscle showing the general distribution of LamAC expression.
- Dystrophin expression through all TA muscles, showing restoration of dystrophin protein production in DMD muscles.

- **Quantative analysis of dsytrophin restoration.**



- WB analysis of TA at four weeks post-implantation revealed robust dystrophin expression, reaching approximately 40% of WT healthy muscle levels, together with α-sarcoglycan expression.
- Quantification of cell engraftment level by counting the number of LamAC+ cells, showing persistent expression in muscle transplanted with U7-hMabs after 8 weeks of scaffold implantation, while there was a significant reduction of wt.hMabs.

Acknowledgements

The authors would like to thank Sarah Cartmell, Mohamed Elsawy, and the Henry Royce Institute for Advanced Materials (grant no. EP/R00661X/1, EP/S019367/1, EP/P025021/1, and EP/P025498/1) for support and equipment use. We acknowledge the bioimaging, and electron microscopy (EM-FMBH) facilities at the University of Manchester for providing access to Confocal Leica SP8, and SEM which were instrumental in the completion of this research.

Fund

This work was supported by MRC grant R132096, the Wellcome Trust HICF, the ERC-AIG Unimab, the ERC PoC Unicardiomab to GC, the Astra Zeneca- MRC grant to FG, and by full scholarship [MM38/19] awarded to Amer. S. from The Egyptian Ministry of Higher Education & Scientific Research represented by The Egyptian Bureau for Cultural & Educational Affairs in London.