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TERG TISSUE ENGINEERING RESEARCH GROUP

AMBER

3D BIOMATERIAL SCAFFOLD-BASED DELIVERY PLATFORMS FOR ENHANCED TISSUE REPAIR

Prof. Fergal J. O'Brien PhD, FAS, FEAMBES, CEng, FIEI, MRIA

Professor of Bioengineering & Regenerative Medicine
Director of Research & Innovation, RCSI
Head of Tissue Engineering Research Group
Deputy Director, Advanced Materials & BioEngineering Research (AMBER) Centre

Dept. of Anatomy & AMBER Centre,
Royal College of Surgeons in Ireland

@fjobrien @TissueEngDublin @AmberCentre

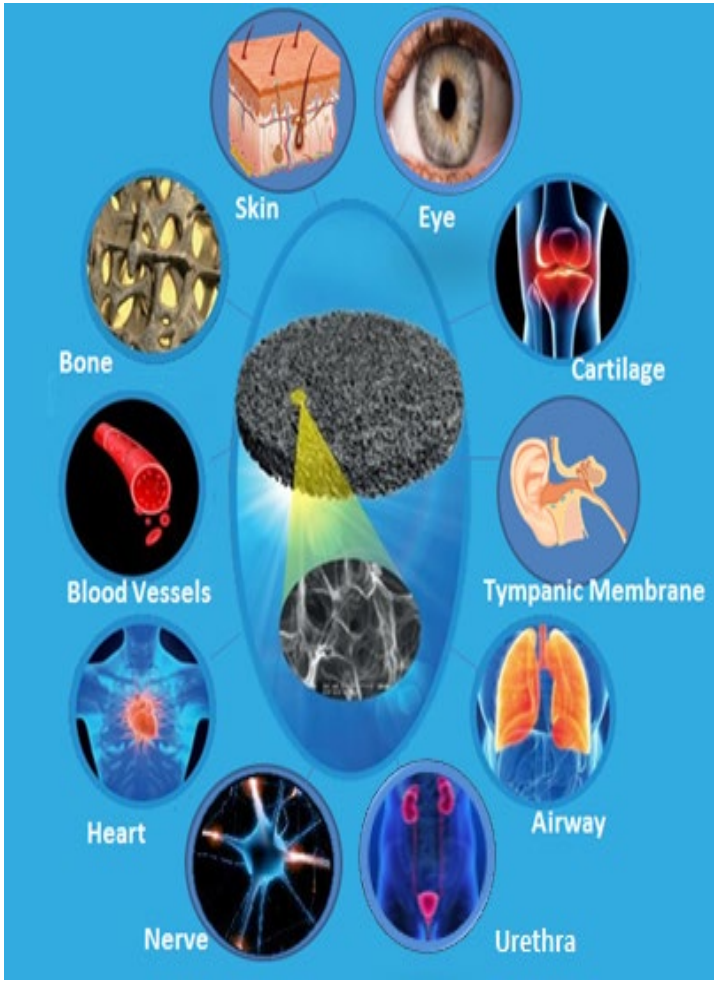
Royal College of Surgeons in Ireland (RCSI)

Independent College of Health Sciences
Founded 1784

RCSI Research Mission: ***"Research informed by clinical problems, translated into better therapies and interventional strategies for the benefit of patients"***

Research Mission

Biomimetic biomaterial scaffolds as therapeutics to regenerate organs and as a pathophysiology models for disease & drug screening



Designer ECM-based Scaffolds for Tissue Repair

- Altered composition
  (including addition of GAGs, ceramic, elastin, chitosan, alginate, fibrin)

Tierney CM+ (2009) JMBBM 2(2): 202-209.
Tierney CM+ (2009) JBMR:A 91A(1):92-101.
Alhag+ (2011) Oral & Maxillofacial Surg 15(1):31-9.
Lyons F+ (2010) Biomaterials 31(35):9232-43.

- Altered crosslinking to improve scaffold mechanical properties

Keogh MB + (2011) Biotechnology & Bioengineering 108(5): 1203-1210
Keogh MB + (2010) Acta Biomaterialia 6(11):4305-13.
Keogh MB + (2010) Cell and Tissue Research 340(1): 169-177.
Haugh MG + (2011) Tissue Engineering: A 17(9-10):1201-8.
Haugh MG + (2010) Tissue Engineering: C 16(5):887-94.
Haugh MG + (2010) JBMR:A 89A(2): 363-369.

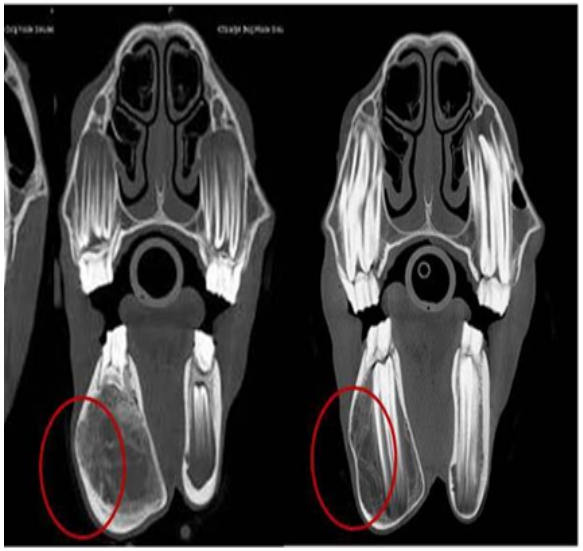
- Altered scaffold pore size

Murphy CM + (2011) JMBBM 11: 53–62.
Murphy CM & O'Brien FJ (2010) Cell Adhesion & Migration 4(3): 377-381.
Murphy CM + (2010) Biomaterials 31: 461–466
Byrne EM+ (2008) J Materials Science: Materials in Medicine 19(11): 3455-3463.

Collagen-hydroxyapatite scaffolds as a viable alternative to bone grafting

nent of HydroxyColl: Equine Case Study
oughbred filly with large cystic lesion (right mandible)
d resumption of racing activity within 12 months

2 Months 14 Months



J.; de Swarte, M.; Jahns, H.; Gleeson, J.P. and O'Brien, F.J.
Engineering & Regenerative Medicine. Oct;9(10):1193-9.

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US & EU I

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SurgaColl
Surgical Innovation delivered naturally

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Cartilage Repair

- Damage to cartilage frequently occurs due to disease and sporting injury
- Cartilage has poor regenerative ability
- Can lead to the requirement for joint replacement
- Treatments include:
  - Microfracture
  - Mosaicplasty
  - Autologous Chondrocyte Implantation

Microfracture Technique

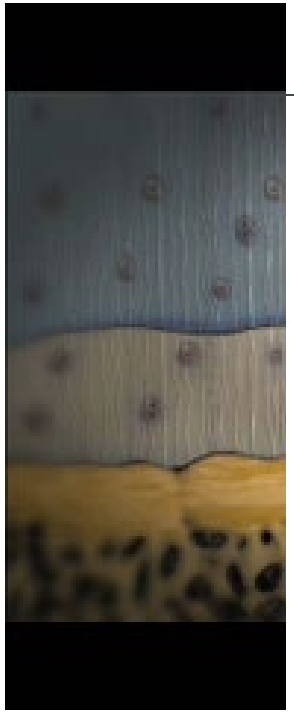
Mosaicplasty

Autologous Chondrocyte Implantation (ACI)

➢ **Current techniques do not result in long term success**

Multi-layered colla repair of focal lesi

- Designed to replicate na
- Fabricated using an “iter
- Interconnected pore stru



Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

Multi-layered collagen-based scaffolds for osteochondral defect repair in rabbits

Tanya J. Levingstone [a,b,c,1], Emmet Thompson [a,b,c,1], Amos Matsiko [a,b,c], Alexander Schepens [d], John P. Gleeson [a,b,c,e], Fergal J. O'Brien [a,b,c,*]

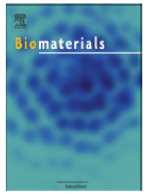
[a] Tissue Engineering Research Group, Dept. of Anatomy, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland
[b] Trinity Centre for Bioengineering, Trinity College Dublin, Dublin 2, Ireland
[c] Advanced Materials and Bioengineering Research (AMBER) Centre, RCSI & TCD, Ireland
[d] Department of Orthopaedic Surgery, AZ Sint-Lucas Hospital, Ghent, Belgium
[e] SurgaColl Technologies Ltd., Invent Centre, Dublin City University, Dublin, Ireland

Biomaterials 87 (2016) 69–81

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials



Cell-free multi-layered collagen-based scaffolds demonstrate layer specific regeneration of functional osteochondral tissue in caprine joints

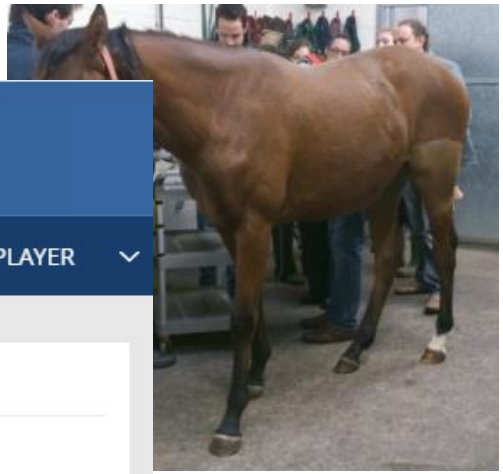
Tanya J. Levingstone [a, b, c], Ashwanth Ramesh [a, b, c, 1], Robert T. Brady [a, b, c, 1], Pieter A.J. Brama [d], Clodagh Kearney [d], John P. Gleeson [a, b, c, e], Fergal J. O'Brien [a, b, c, *]

[a] Tissue Engineering Research Group, Department of Anatomy, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland
[b] Trinity Centre for Bioengineering, Trinity College Dublin, Dublin 2, Ireland
[c] Advanced Materials and Bioengineering Research (AMBER) Centre, RCSI & TCD, Ireland
[d] Section Veterinary Clinical Sciences, School of Veterinary Medicine, University College Dublin, Dublin, Ireland
[e] SurgaColl Technologies Ltd., Invent Centre, Dublin City University, Dublin, Ireland

[1] US & EU Patent (Granted)
[2] Levingstone *et al*, (2014), *Acta Biomater.* 10(5):1996-2004

1st Clinical Assessment of ChondroColl

- Equine Case
  - 16 mo filly
  - Left ≈ 40 x



RTÉ News

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Science and Technology

Irish scientists discover material to repair cartilage

0 | 1045

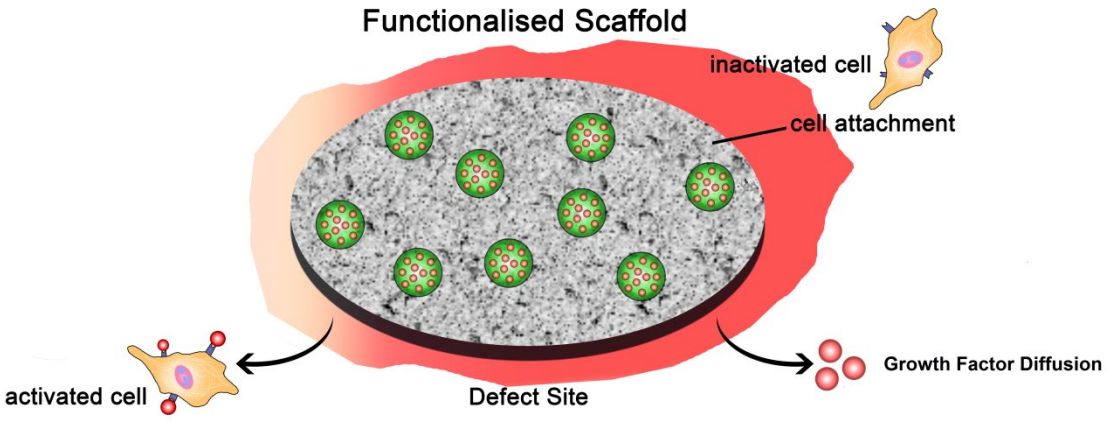
Thursday 19 May 2016 21.10

Stack, J.D.; Levingstone, T.J. et al (2017) Repair of large osteochondritis dissecans lesions using a multi-layered collagen-based osteochondral graft substitute in an equine athlete. *J Tissue Engineering & Regenerative Medicine* Oct;11(10):2785-2795.


12 02

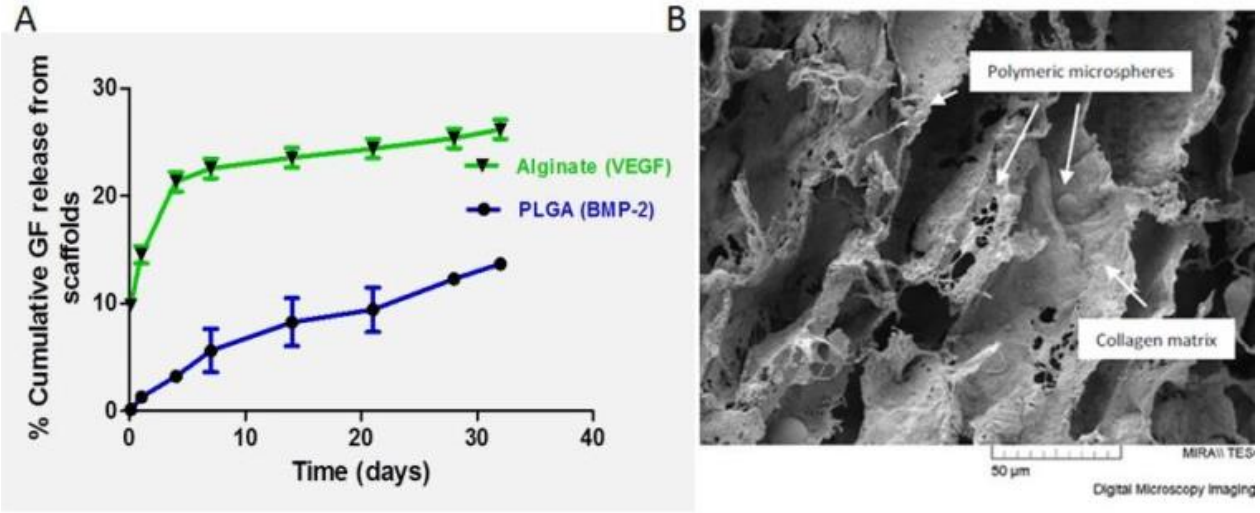
Clinical Need for Advanced Therapeutics

- In order to heal very large defects in humans an extra stimulus may be required
- Stem cells, biomolecules/drugs (antibiotics, growth factors & genes)
- Safe, effective delivery systems needed
- Scaffolds for controlled, sustained, transient release of therapeutic biomolecules

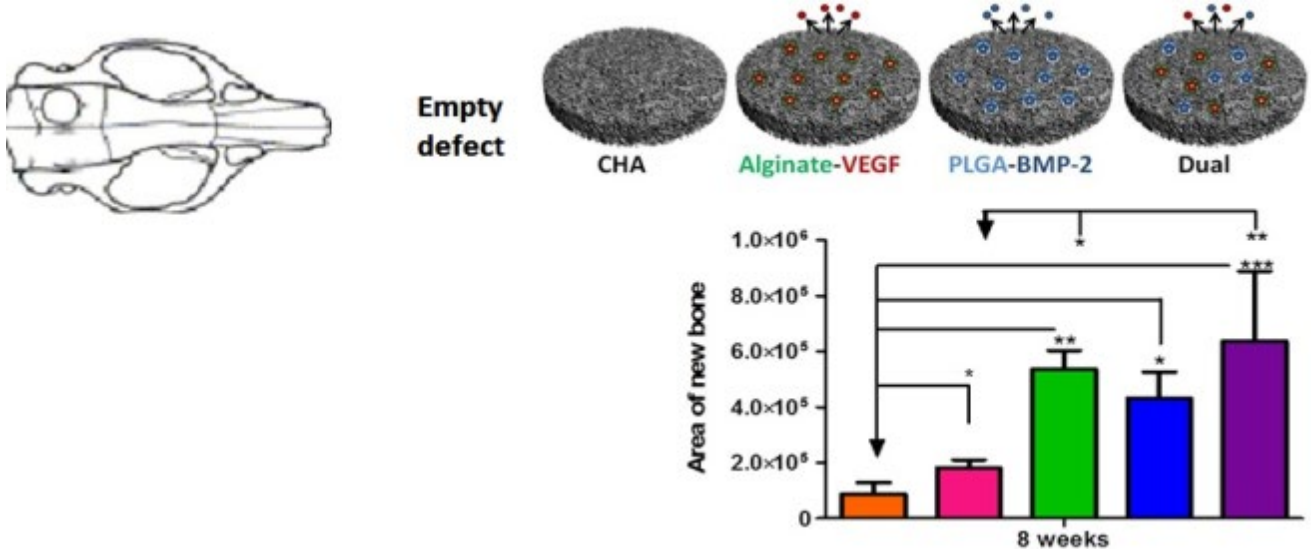


Scaffolds as Drug Delivery Systems

- Growth factors/recombinant proteins/antibiotics



(A) Controlled release of BMP & VEGF from a collagen-based scaffold at two different rates using two different types of polymeric microcapsules (B) SEM image of growth factor-containing microparticles embedded in the collagen matrix of the scaffold

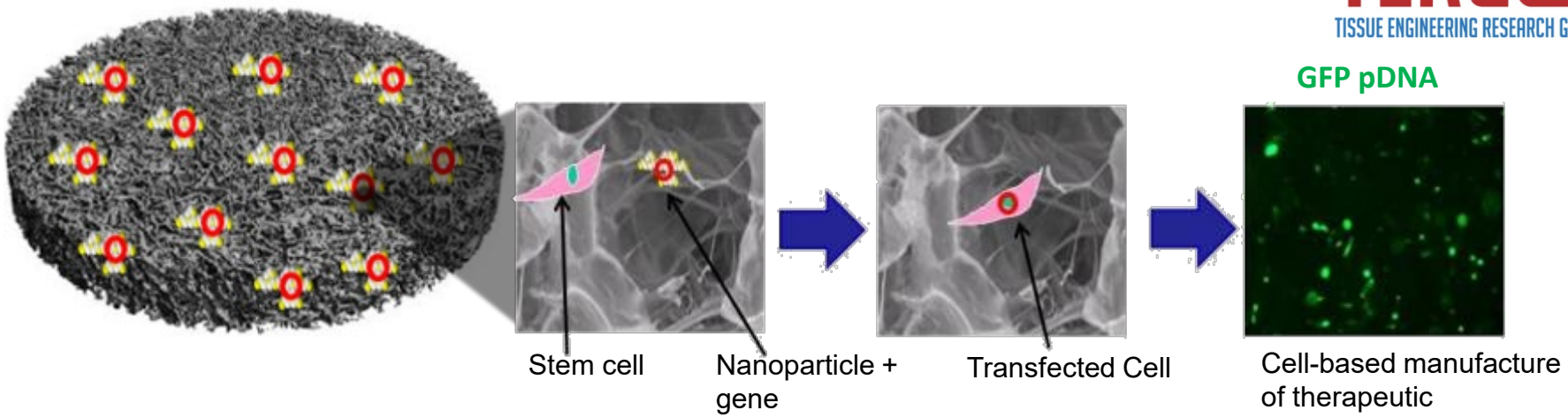


Quinlan et al. Journal of Controlled Release 2015: 10;207:112-9.
Quinlan et al. Journal of Controlled Release 2015 198C:71-79

Gene-activated Scaffolds

- Gene-activated scaffolds as an efficient alternative to protein delivery
- Nucleic acids: pDNA/ siRNA/ microRNAs & mRNAs (non-viral technologies)
- By delivering genes, the protein can be released in a sustained and controllable manner i.e. the cells act as a drug factory

Non-viral gene-activated Scaffolds



- PEI
Polyethyleneimine

Tierney et al. (2012) *Journal of Controlled Release* 158(2):304-11
Tierney et al. (2013) *Journal of Controlled Release* 165(3):173-82
Tierney et al. (2013) *Organogenesis.* 9(1). 158-164
Laiva et al. (2018) *International Journal of Pharmaceutics.* 544(2):372-379.

- Cell penetrating peptides (GET: Shakesheff/Dixon, RALA: Nottingham & McCarthy, QUB)

- New materials (CURAM and AMBER)
- Star-shaped dendrimers
- Layered double hydroxides

Walsh et al (2017) *Gene Therapy.* doi: 10.1038/gt.2017.58
Walsh et al (2018) *Molecular Pharmaceutics* . 7;15(5):1878-1891

- Chitosan

Raftery et al. (2015) *Journal of Controlled Release* 210: 84–94
Raftery et al. (2016) *Advanced Materials* 28(27):5447-69
Raftery et al. (2017) *Biomaterials* 149:116-127.
Raftery et al. (2018) *Journal of Controlled Release* 283:20-31

- Hydroxyapatite nanoparticles

Curtin et al. (2012) *Advanced Materials. 24*(6):749-54
Curtin et al. (2015) *Advanced Healthcare Materials.* 4(2):223-7

Gene-activated scaffolds: nano-HA particles as non-viral delivery vectors

ACS APPLIED MATERIALS & INTERFACES

Research Article

www.acsami.org

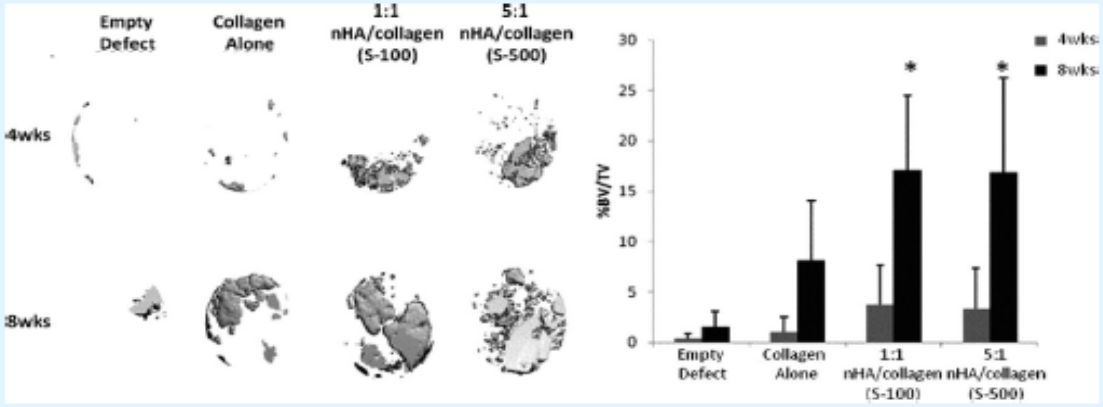
Content-Dependent Osteogenic Response of Nanohydroxyapatite: An in Vitro and in Vivo Assessment within Collagen-Based Scaffolds

Gráinne M. Cunniffe,[†,‡,⊥] Caroline M. Curtin,[†,‡,§,⊥] Emmet M. Thompson,[†,‡,§] Glenn R. Dickson,[§] and Fergal J. O'Brien*[,†,‡,§]

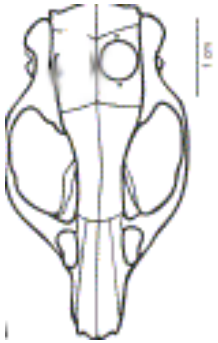
[†]Trinity Centre for Bioengineering, Trinity College Dublin, Dublin 2, Ireland

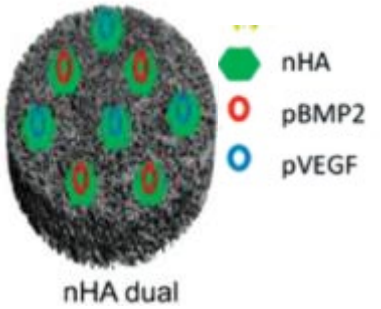
[‡]Advanced Materials and BioEngineering Research Centre, Royal College of Surgeons in Ireland & Trinity College Dublin, Dublin 2, Ireland

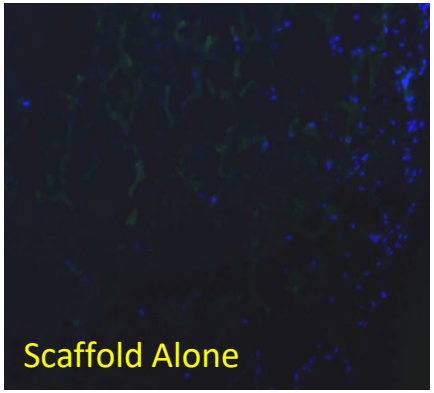
[§]Tissue Engineering Research Group, Department of Anatomy, Royal College of Surgeons in Ireland, 123 St. Stephens Green, Dublin 2, Ireland

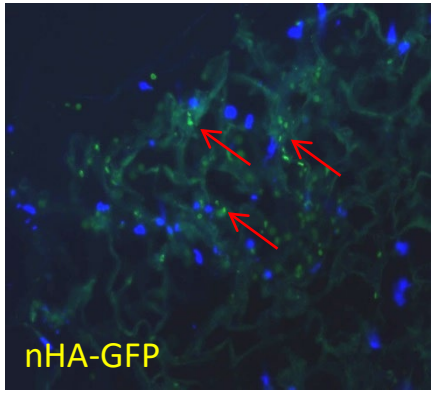


Combinatorial Gene Therapy Enhancing Osteogenesis & Angiogenesis







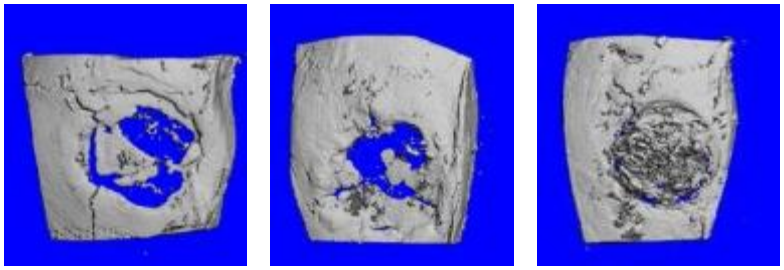


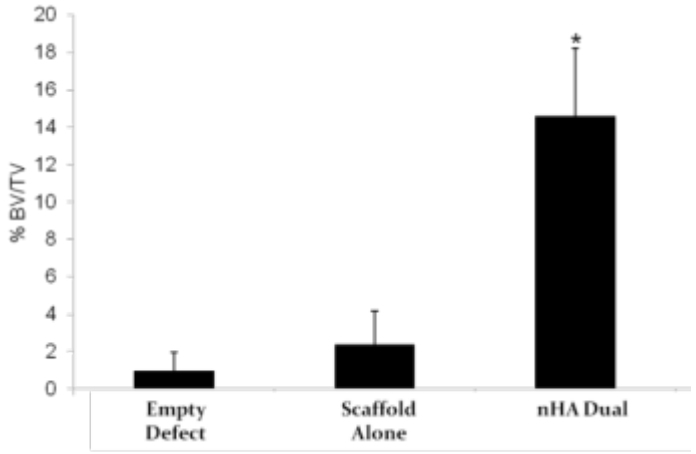
= DAPI stained nucleus

→ = GFP expressing cell

GFP expression 1 wk post implantation showing **host cell** migration, infiltration and transfection

Empty Defect | Scaffold Alone | BMP2/VEGF





MicroCT Analysis
4 weeks post-implantation

Curtin et al. 2015 *Advanced Healthcare Materials* 4(2):223-7.

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microRNA-activated scaffolds

Journal of Controlled Release 200 (2015) 42–51

Contents lists available at ScienceDirect

Journal of Controlled Release

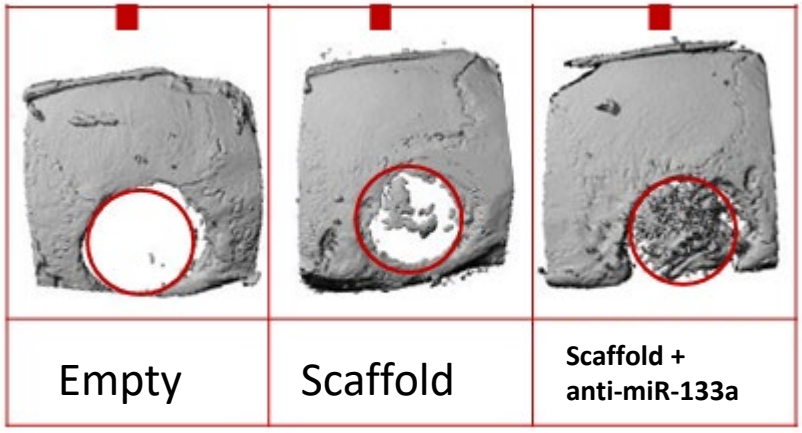
journal homepage: www.elsevier.com/locate/jconrel

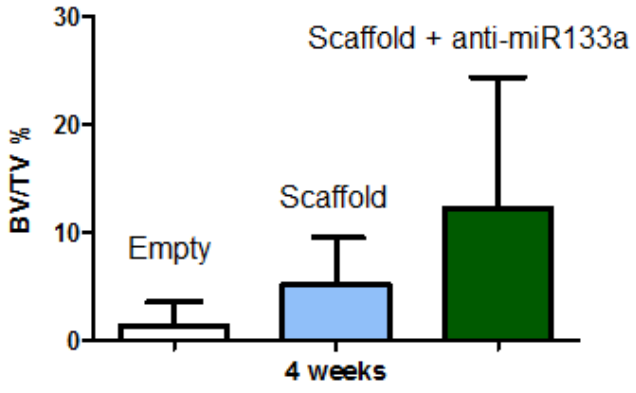
A novel collagen-nanohydroxyapatite microRNA-activated scaffold for tissue engineering applications capable of efficient delivery of both miR-mimics and antagomiRs to human mesenchymal stem cells

Irene Mencía Castaño [a,b,c], Caroline M. Curtin [a,b,c], Georgina Shaw [d], J. Mary Murphy [d], Garry P. Duffy [a,b,c,*], Fergal J. O'Brien [a,b,c,*]

[a] Tissue Engineering Research Group, Department of Anatomy, Royal College of Surgeons in Ireland, 123 St. Stephens Green, Dublin 2, Ireland
[b] Trinity Centre for Bioengineering, Trinity College Dublin, College Green, Dublin 2, Ireland
[c] Advanced Materials and Bioengineering Research (AMBER) Centre, RCSI & TCD, Dublin 2, Ireland
[d] Regenerative Medicine Institute, National University of Ireland, Galway, Ireland

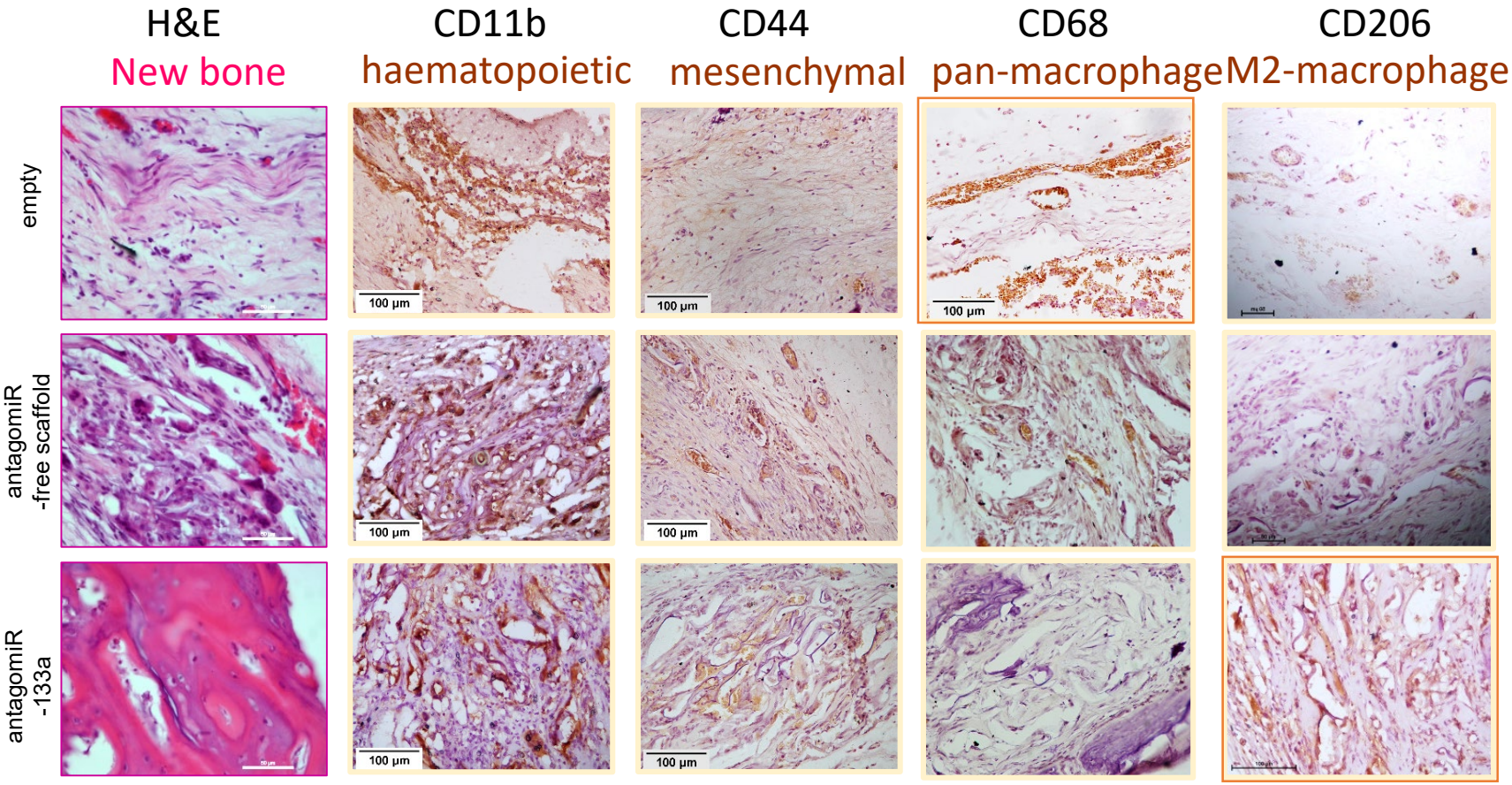
micoRNA-mediated bone repair after just 4 weeks (anti-miR-133a)





Mencía Castaño et al. 2019, *In Review*

Host cell response to miR-mediated bone repair after 4 weeks (antagomiR-133a):



no differences based on treatment

Inverted trends based on treatment

antagomiR-133a treatment showed fewer pan-macrophages & more M2- (pro remodelling) macrophages

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Chitosan as a vector for gene delivery in orthopaedics

Acta Biomaterialia 43 (2016) 160–169

Contents lists available at ScienceDirect

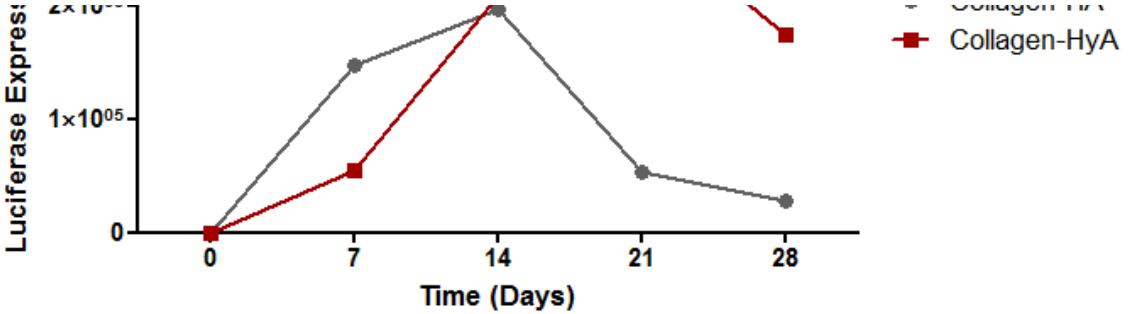
Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

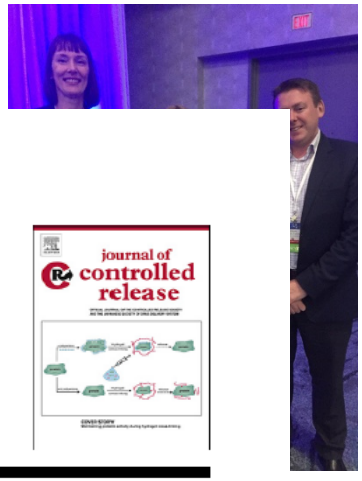
Multifunctional biomaterials from the sea: Assessing the effects of chitosan incorporation into collagen scaffolds on mechanical and biological functionality

Rosanne M. Raftery [a,b,c], Brian Woods [a,b,c], Ana L.P. Marques [d,e], Joana Moreira-Silva [d,e], Tiago H. Silva [d,e], Sally-Ann Cryan [a,b,f], Rui L. Reis [d,e], Fergal J. O'Brien [a,b,c,*]



Raftery et al. (2015) *Journal of Controlled Release* 210: 84–94

Chitoson as a gene delivery vector



Journal of Controlled Release 283 (2018) 20–31

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Delivery of the improved BMP-2-Advanced plasmid DNA within a gene-activated scaffold accelerates mesenchymal stem cell osteogenesis and critical size defect repair

Rosanne M. Raftery[a,b,c], Irene Mencía-Castaño[a,b,c], Simon Sperger[d], Gang Chen[e], Brenton Cavanagh[f], Georg A. Feichtinger[g], Heinz Redl[d], Ara Hacobian[d], Fergal J. O'Brien[a,b,c,*]

[a] Tissue Engineering Research Group, Dept. of Anatomy, Royal College of Surgeons in Ireland, Dublin, Ireland
[b] Trinity Centre for Bioengineering, Trinity College Dublin, Dublin, Ireland
[c] Advanced Materials and Bioengineering Research Centre (AMBER), RCSI and TCD, Dublin, Ireland
[d] Ludwig Boltzmann Institute for Experimental and Clinical Traumatology/AUVA Research Center, The Austrian Cluster for Tissue Regeneration, European Institute of Excellence on Tissue Engineering and Regenerative Medicine Research (Expertissues EEIG), Vienna, Austria

Translating the role of osteogenic-angiogenic coupling in bone formation: Highly efficient chitosan-pDNA activated scaffolds can accelerate bone regeneration in critical-sized bone defects

Rosanne M. Raftery [a, b, c, d], Irene Mencía Castaño [a, b, c], Gang Chen [e], Brenton Cavanagh [f], Brian Quinn [a], Caroline M. Curtin [a, b, c], Sally Ann Cryan [a, b, d], Fergal J. O'Brien [a, b, c, *]

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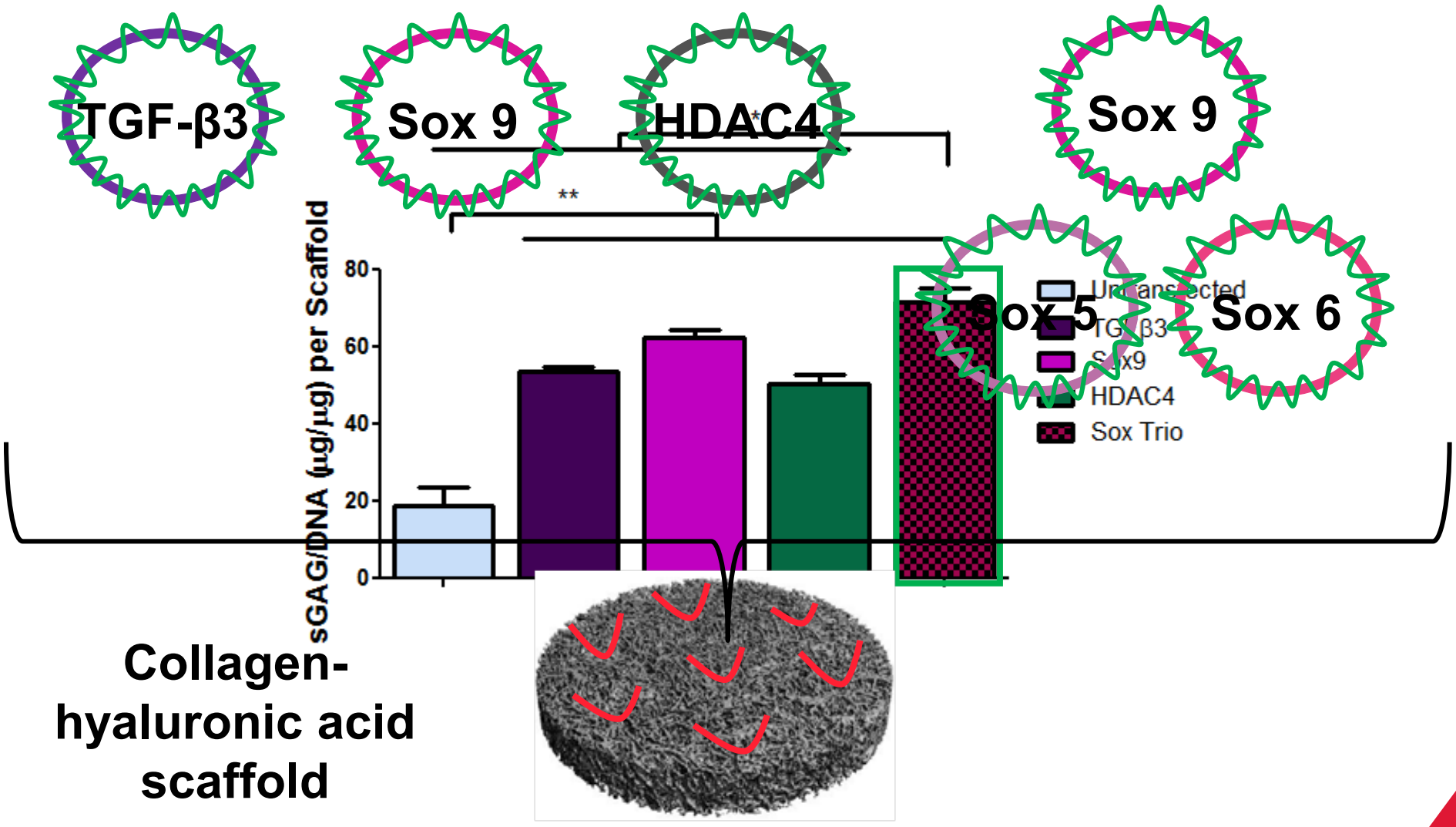
[b] Trinity Centre for Bioengineering, Trinity College Dublin, Dublin, Ireland
[c] Advanced Materials and Bioengineering Research Centre (AMBER), RCSI and TCD, Dublin, Ireland
[d] School of Pharmacy, Royal College of Surgeons in Ireland, Dublin 2, Dublin, Ireland
[e] Department of Physiology and Medical Physics, Centre for the Study of Neurological Disorders, Microsurgical Research and Training Facility (MRTF), Royal College of Surgeons in Ireland, Dublin, Ireland
[f] Cellular and Molecular Imaging Core, Royal College of Surgeons in Ireland, Dublin, Ireland

Gene-activated scaffold for cartilage repair



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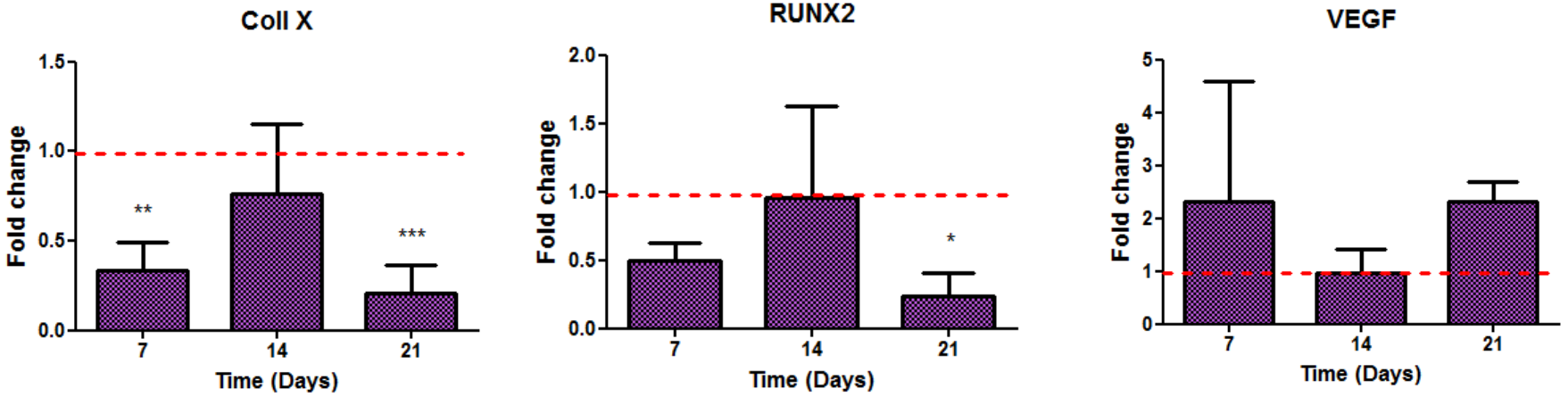
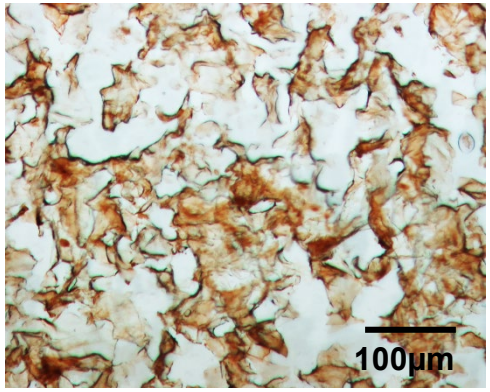
Sox trio-activated scaffold inhibits hypertrophy and enhances chondrogenesis

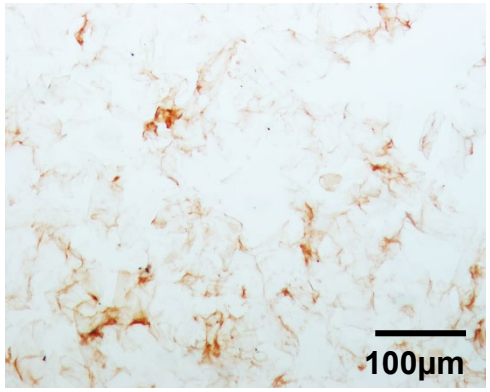


Collagen type X

Gene-free Scaffold



Gene-activated Scaffold



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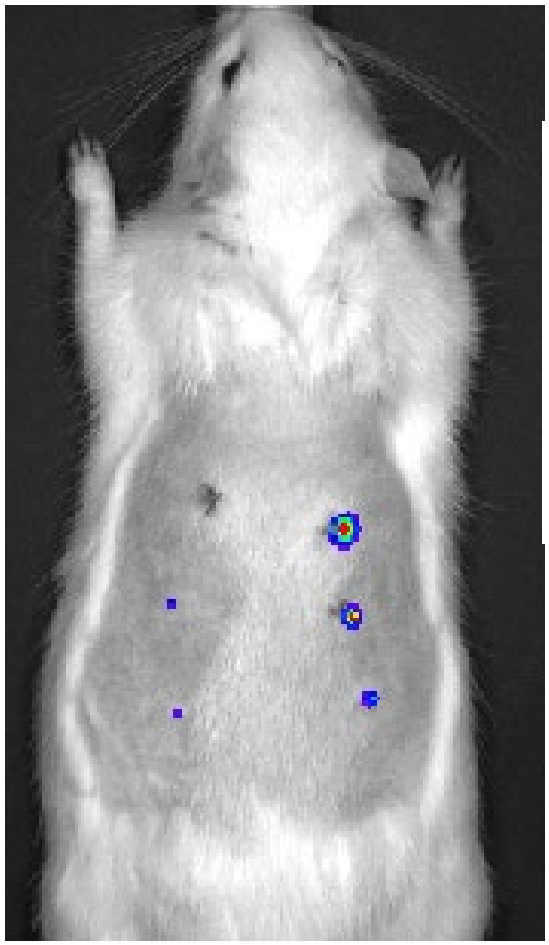
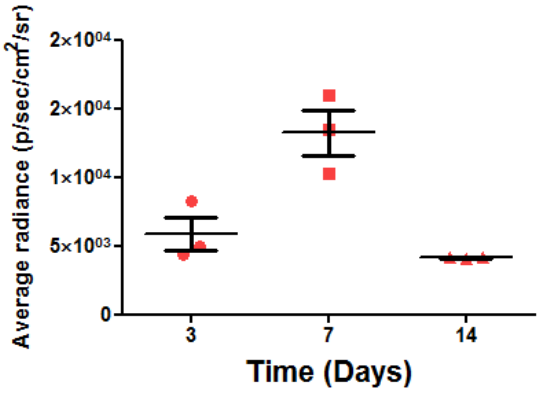
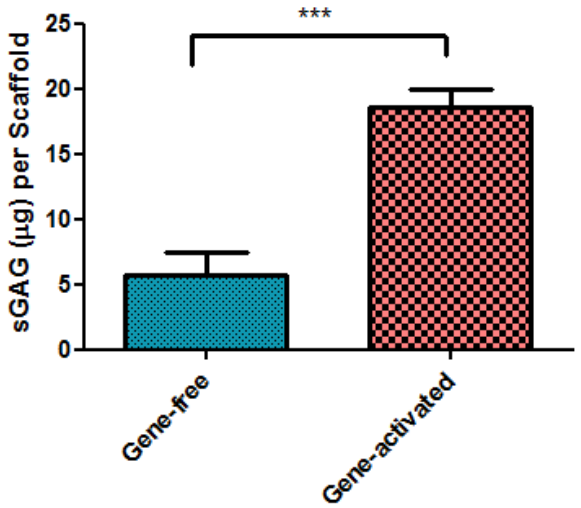
Sox trio-activated scaffold can transfect host cells and enhance cartilage formation *in vivo*





Gene-activated scaffold capable of safe, efficient, localised but transient transfection of host cells *in vivo*



Gene-activated scaffold promotes the formation of stable cartilage in vivo

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ERC Advanced Grant €3million 2018-2022

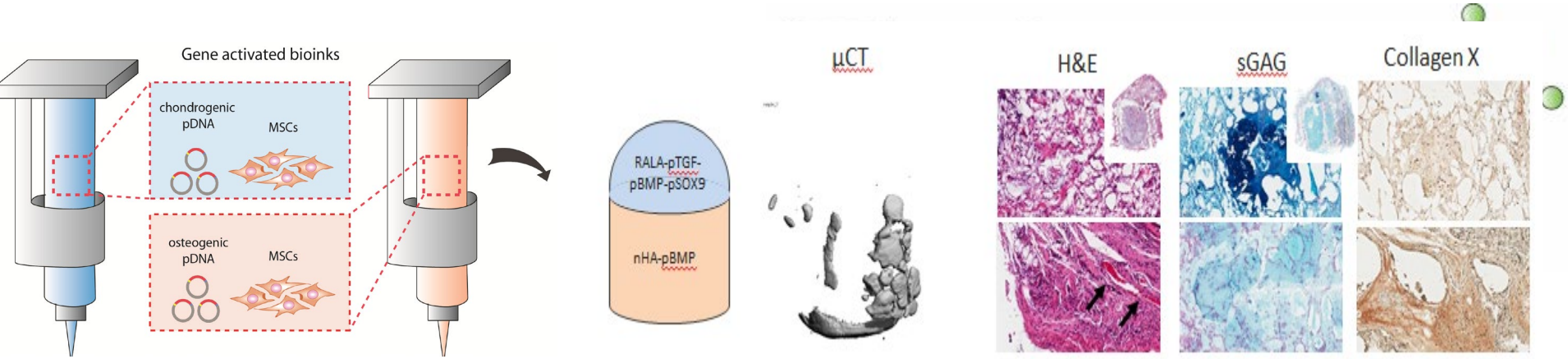
RECAP. Regeneration of Articular Cartilage using Advanced Biomaterials and Printing Technology

- Combines 3D printing of biomaterials with world class expertise in natural polymers & gene activated scaffolds to develop a paradigm shifting approach to articular joint repair

Kick Off: Autumn 2018 **We're Hiring!!**

Development of pore-forming bioinks for 3D printing of temporally controlled non-viral gene delivery *in vivo*

- Spatially patterned therapeutic ene delivery within mechanically reinfrced osteochondral gene activated constructs can modulate MSC fate zonally *in vivo*



Journal of Controlled Release 301 (2019) 13–27

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Pore-forming bioinks to enable spatio-temporally defined gene delivery in bioprinted tissues

Gonzalez-Fernandez T.[a,b,c], Rathan S.[a,b], Hobbs C.[c,d,e], Pitacco P.[a,b], Freeman F.E.[a,b], Cunniffe G.M.[a,b], Dunne N.J.[a,b,c,f,g,h], McCarthy H.O.[h], Nicolosi V.[c,d,e], O'Brien F.J.[a,c,i], Kelly D.J.[a,b,c,i,*]

Gonzalez-Fernandez+ Tissue Eng Part A. 2016 22(9-10):776-8
Gonzalez-Fernandez+ Acta Biomater 2017 55:226-238.

Skin: Gene-activated collagen-GAG scaffolds to enhance vascularisation, limit fibrosis & improve repair

Approaches

1. Gene-activated scaffold for delivery of pro-angiogenic molecules (VEGF, SDF-1α, FGF) – alone and in combination.

2. Gene-activated scaffolds to inhibit fibrosis (siRNA for MMP-9) in diabetic foot ulcers

3. Gene-activated scaffolds technology for enhanced nerve regeneration

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gene2skin
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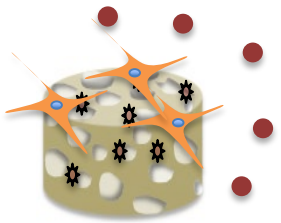
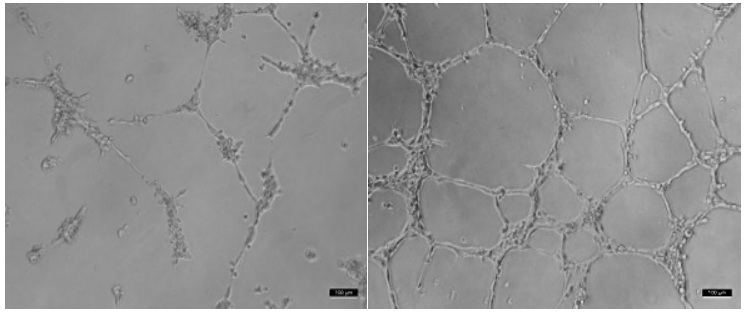
Pro-angiogenic impact of SDF-1α GAS on MSCs (bone marrow & adipose) for wound healing applications



SDF-1α overexpressing MSCs on SDF-1α GAS

Secreted factors →

MSCs + Scaffold | MSCs + SDF-1α GAS



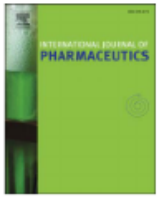
Enhanced endothelial angiogenesis at 12 h

International Journal of Pharmaceutics 544 (2018) 372–379

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm



Pro-angiogenic impact of SDF-1α gene-activated collagen-based scaffolds in stem cell driven angiogenesis

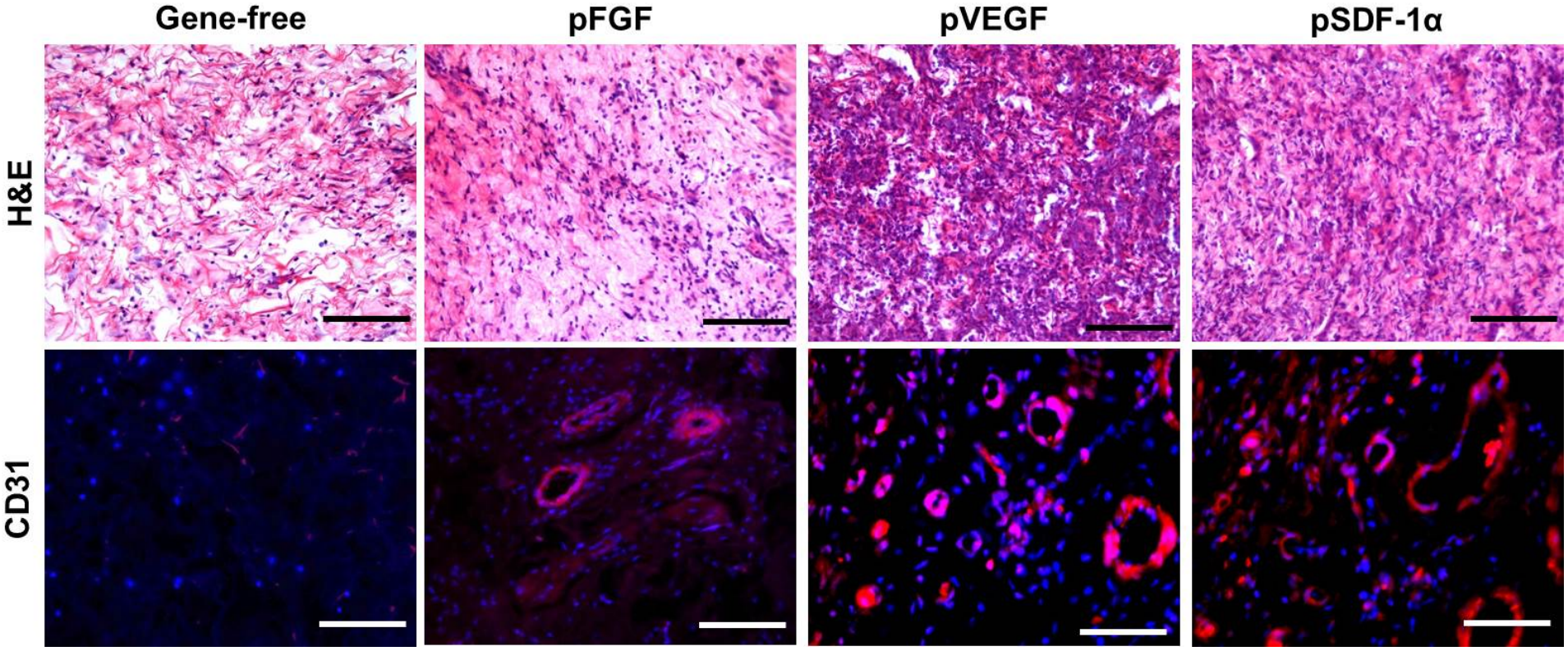
Ashang Luwang Laiva[a], Rosanne M. Raftery[a,b,c], Michael B. Keogh[a,d,*], Fergal J. O'Brien[a,b,c]

[a] Tissue Engineering Research Group, Dept. of Anatomy, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland
[b] Trinity Centre for Bioengineering, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin 2, Ireland
[c] Advanced Materials and Bioengineering Research Centre, Royal College of Surgeons in Ireland and Trinity College Dublin, Dublin, Ireland
[d] Royal College of Surgeons in Ireland-Medical University of Bahrain, Adliya, Bahrain

Significant wound healing response by 24 h

Michael Keogh, RCSI Medical University of Bahrain

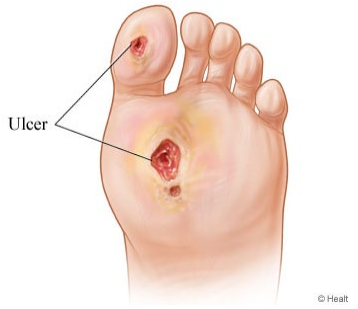
Subcutaneous Implantation of Gene-activated Scaffolds



Raftery et al. 2019 (under review)

Diabetic foot ulcers (DFU)

- ~ 20% diabetic patients may develop DFU [2]
- Many therapies have been tested for DFU healing
- Increased level of matrix metalloproteinases (MMP-9) is one key factor associated with failed healing of DFU [3]



http://www.webmd.com/diabetes/diabetic-foot-ulcer

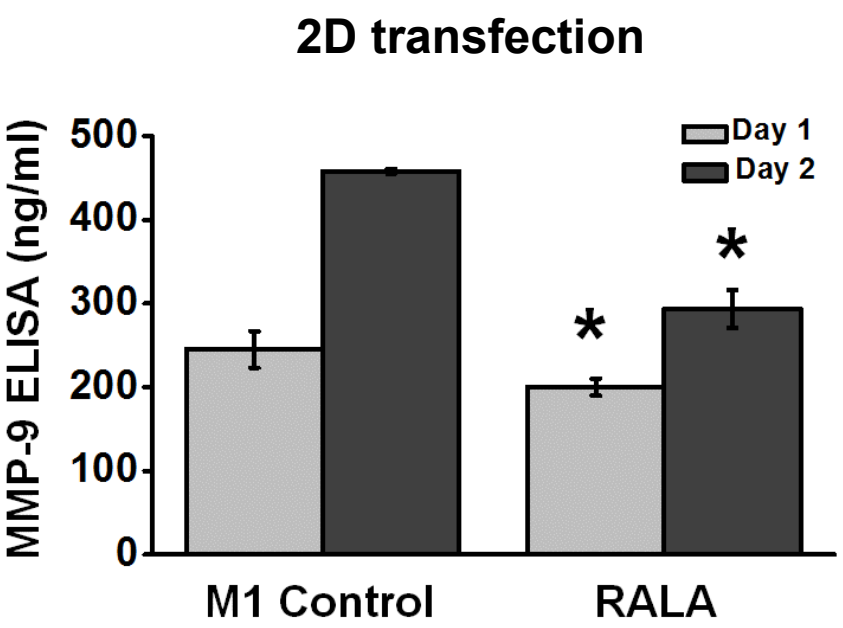
Hypothesis: Downregulation of MMP-9 may be used to improve DFU healing

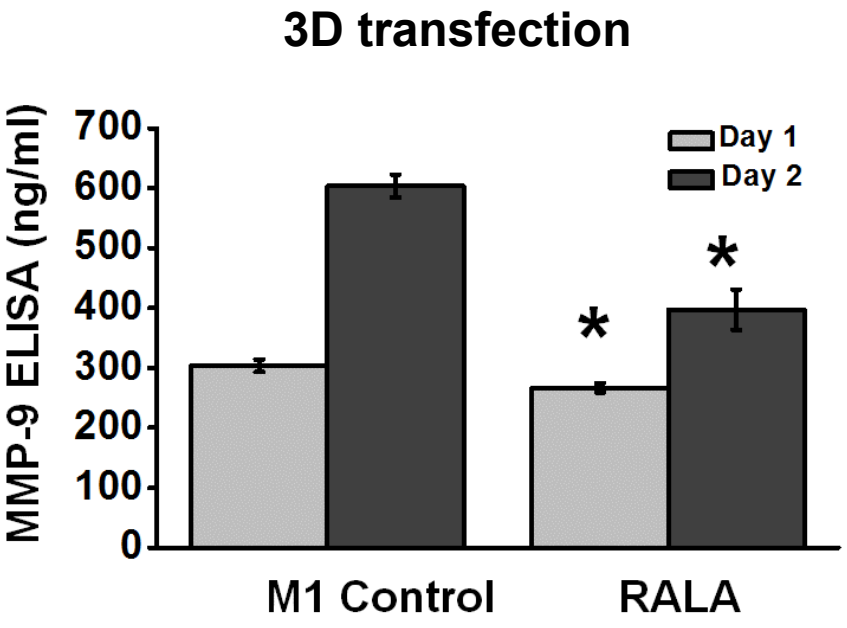
Leping Yan

[1]International Diabetes Federation (2003). Diabetes atlas, 2 edn, International Diabetes Federation, Brussels

[2]Singh N, et al. Jama, 2005, 293: 217-28 [3]Dinh T, et al. Diabetes, 2012, 61: 2937-47

RALA/siMMP-9 response on macrophages





* $P < 0.05$ compared to M1 control on the same timepoint

RALA/-siMMP-9 can downregulate MMP-9 production of M1 macrophages in both 2D and 3D models

Yan et al. 2019 (under review)

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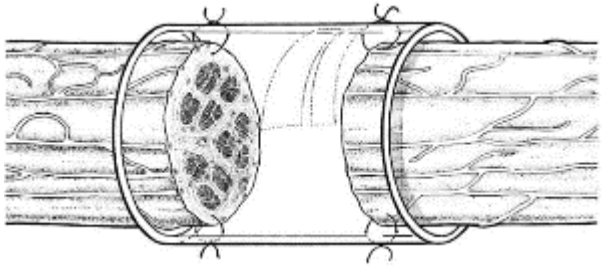
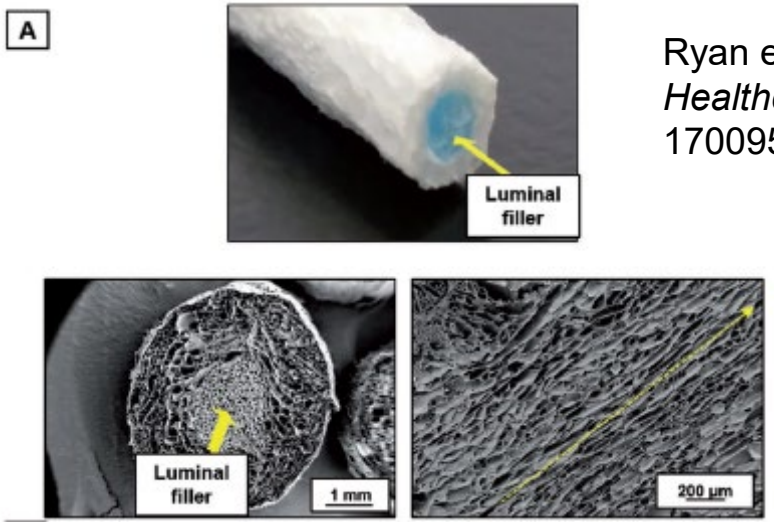
Next Generation Scaffolds as Nerve Guidance Conduits

Problem:
Peripheral nerves damaged frequently due to trauma and disease
Nerve graft from a donor site in the patient themselves used to treat defects but limited in availability

Solution: Incorporate bioactive macromolecules, inherent to nerve tissue, to enhance the regenerative capacity of collagen based scaffold for large defect nerve repair





Ryan et al. *Adv. Healthcare Mater.* **2017**, 1700954 1-13

Patent Filed

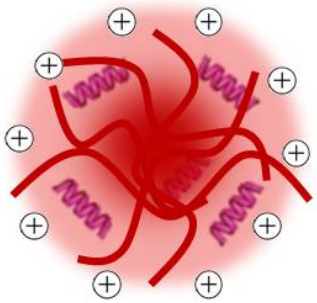
2015: AMBER- Integra Funded Seed Spoke Project: €75,000
2016: AMBER-Integra-SFI Targeted Project: €1.4 million

Gene activated Nerve Guidance Conduits

- **Nerve growth factor (NGF):** Growth and proliferation of neurons
- **Glial derived neurotrophic factor – 2 (GDNF):** Promotes neuron survival
- **JUN**: Encodes for the transcription factor **c-Jun**, activated after peripheral nerve injury
  - regulates the phenotypic switch of Schwann cells from myelinating, to non-myelinating and pro-regeneration
  - Regulates NGF and GDNF transcription

PEI-pGFP

PEI-pGLuc



PEI-pNGF

PEI-pGDNF

PEI-pJun

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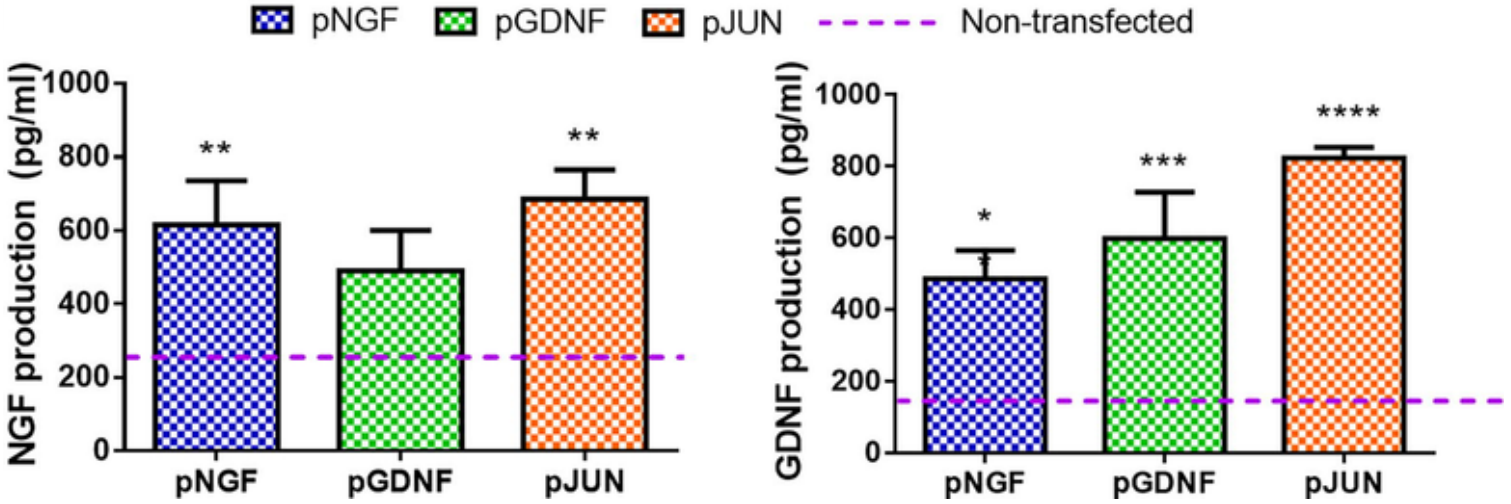
Enhanced Therapeutic Response using Gene Activated NGC



Acta Biomaterialia 75 (2018) 115–128

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

In vitro efficacy of a gene-activated nerve guidance conduit incorporating non-viral PEI-pDNA nanoparticles carrying genes encoding for NGF, GDNF and c-Jun

William A. Lackington [a,b,c], Rosanne M. Raftery [a,b,c], Fergal J. O'Brien [a,b,c,*]

[a] *Tissue Engineering Research Group (TERG), Department of Anatomy, Royal College of Surgeons in Ireland, Ireland*
[b] *Advanced Materials and Bioengineering Research (AMBER) Centre, Trinity College Dublin, Ireland*
[c] *Trinity Centre for Bioengineering (TCBE), Trinity College Dublin, Ireland*

State of the Art & Future Directions

- Gene therapy presents major opportunities for tissue repair for a myriad of indications
- Application (and cell) tailored optimisation of vectors needed
- Gene-activated scaffolds provide an opportunity to deliver cargo in a sustained, controllable but transient manner i.e. effective but safe
- 3D printing may provide enhanced scaffolds and spatio-temporal gene delivery for complex tissues

Acknowledgements

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