Researcher (s):	Prof Fergal O'Brien
Research Institution:	Royal College of Surgeons Ireland
Project Title:	Gene-activated scaffolds for the treatment of EB
Research Area:	Gene Therapy
Start Date: Mar 2023	End Date: Aug 2023
Funded by:	DEBRA Ireland

Lay Summary

Epidermolysis Bullosa (EB) is a rare genetic condition affecting around 1 in every 30,000 babies globally, with 1 in 18,000 children born in Ireland having the condition. In patients with EB defected genes make skin so fragile that it can tear or blister at very slight provocation. It has also been linked to development of many other health complications. In this project we propose the unique combination of gene therapy to tackle the defected gene, with tissue engineering to build biomaterial scaffolds designed for successful healing of EB skin tears or lesions. In essence, we are suggesting the future use of a gene-activated scaffold as an off-the-shelf treatment for EB wounds, acting as a dressing and potential antibacterial agent for external wounds and blisters.

Usually in gene therapy, viruses are used to deliver genes to cells, which can face safety and regulatory concerns. Instead, we will use a technology we describe as a 'gene-activated scaffold' containing nanoparticles housing corrected forms of the defected genes which will be delivered to target cells, both safely and efficiently. Following on from the successful gathering of preliminary data in this project in two- and three-dimensional *in vitro* models, we will apply for funding for a larger grant with the aim of further testing of these scaffolds including analysis in *in vivo* environments. Our ultimate goal is for our gene-activated scaffolds to be implanted into an EB skin lesion, where the patient's own cells will migrate into it, collect the loaded nanoparticles and start using the corrected gene to enhance regeneration.

Reducing wound severity, risk of infection and accelerating wound healing are top priorities for patients living with EB and their caregivers (Bruckner et al, 2020). Our research has not only the potential to reduce wounds but our gene-activated scaffold technology also has anti-microbial properties to avoid unwanted wound infections. Therefore, our off-the-shelf gene-activated scaffolds will be capable of inducing

successful wound healing in EB lesions while limiting infection. This wound closure and avoidance of unwanted infection may also prevent development of other complications.

As we move from the pilot project into implementation in a larger follow on study, PPI will become a major focus of the work. We will collaborate with patient advocates, carers and clinicians to shape this research in meaningful ways including prioritisation of which type of EB to pilot the gene activated scaffolds, project evaluation design and how best to communicate the research process and outcomes to both patients and health policy makers.

Project Abstract

Epidermolysis bullosa (EB), a genetic disorder characterised by ulcerated skin blisters, causes severe pain to patients. Various gene mutations cause different levels of wound occurrence and severity. The more severe forms of EB can require up to 4 hours per day of wound care management requiring significant caregiver assistance. Patients with EB and their carers rank '*reducing the number and severity of wounds as the most important treatment factor'* to improve the quality of their lives (Bruckner et al 2020).

Gene therapy is at the forefront of regenerative medicine strategies for treating EB skin lesions since EB is caused by mutations in specific genes hampering epidermal keratinisation (EB simplex – EBS), disrupting the basement membrane and the homeostasis of the dermal- epidermal junction (junctional EB – JEB; and dystrophic EB - DEB).

However usually in gene therapy, viruses are used to deliver genes to cells, causing safety and regulatory concerns. Our group has an international profile in functionalising collagen- based scaffolds with non-viral vectors (nanoparticles) carrying nucleic acids (pDNA, siRNA, miRNA) to enhance their wound healing potential. We propose in this project to implant these 'gene-activated scaffolds' into an EB skin lesion in order to introduce corrected versions of target genes to cells safely and efficiently. Once our gene-activated scaffolds are implanted, the patient's own cells will migrate towards the scaffolds, be transfected with the nanoparticles containing relevant pDNA encoding for the specific protein. Then will then synthesise the corrected version of the respective protein (such as collagen type VII) for successful healing of the wound.

A major focus of the research is to involve patients and carers in the governance, design and dissemination phases to ensure this technology is translated to benefit

those with chronic and severe wound pain due to EB, and to illuminate the value of PPI in biomedical research.

Blog post written about project for website

*Not blog but part of project application: 'How this project will make a difference to the lives of those with EB and their families'

EB is a rare genetic disorder with global incidence estimated at 1 in 30,000, affecting around 500,000 patients worldwide. Survival beyond infancy is rare for most severe types of EB, and there are currently no cures nor approved treatments specifically for EB.

We are proposing the development of a novel off-the-shelf technology for the treatment of EB lesions based on a combination of gene therapy and tissue engineering biomaterials. The treatment we propose would significantly enhance the quality of life of patients globally if successful. As an off-the-shelf treatment it goes far beyond an ordinary wound dressing. The use of nanoparticle-loaded collagen scaffolds for implantation into EB wounds would facilitate enhanced wound healing with the corrected version of the defective genes in question for each subtype of EB. When combined with the fact that these scaffolds are already proven to have antimicrobial properties which would reduce the incidence of unwanted infections, this would be a huge step forward in treatment of EB.

Importantly, this overall project envisages a profound involvement with patients and carers. This pilot project will begin to develop a structured plan for PPI which will be actively implemented during the course of a follow on project. By combining in a single platform gene therapy, tissue engineering and antimicrobial properties in a novel gene-activated scaffold, this project has potential for commercial and clinical translation, therefore greatly benefitting the lives of patients with EB worldwide.

Quotes we have from Researchers

None

Researcher (s) Bio

Prof. Fergal O'Brien is Professor of Bioengineering & Regenerative Medicine, Deputy Vice Chancellor for Research & Innovation, and Head of Tissue Engineering Research Group in RCSI, one of the largest advanced biomaterials and tissue engineering/regenerative medicine research groups in Ireland. Following a degree in mechanical engineering and PhD in bone mechanobiology, Prof. O'Brien was a

Fulbright Scholar in tissue engineering at Massachusetts Institute of Technology and Harvard Medical School. Since his faculty appointment in 2003, he has published over 260 journal articles in leading peer-reviewed international journals, filed 20 patents/disclosures and supervised over 40 doctoral students to completion. He has a current h-index of 82 (July 2022; Google Scholar). He is a recipient of three prestigious European Research Council Awards (Starting Grant, Proof-of-concept and most recently in 2018, a €3 million Advanced Grant). Other accolades include a Fulbright Scholarship (2001), New Investigator Recognition Award by the Orthopaedic Research Society (2002), Science Foundation Ireland, President of Ireland Young Researcher Award (€1.1. million, 2004), Anatomical Society New Fellow of the Year (2014), Fellowship of both Engineers Ireland (2013) and the European Alliance for Medical & Biological Engineering Science (2016). In 2021, he was invited to contribute to the Interacademy partnership (IAP) Statement on Regenerative Medicine, and was also appointed by invitation to the RIA Charlemont Grant review committee. In 2018, O'Brien was elected as member of the Royal Irish Academy (RIA), Ireland's foremost body of experts in the Sciences and Humanities. He was also awarded the RAMI Silver Medal and presented the Samuel Haughton Honorary Lecture at the 2018 Annual Meeting of the RAMI Section of Bioengineering (BinI). O'Brien is currently a member of the World Council of Biomechanics and immediate-past President of the Section of Bioengineering of the Royal Academy of Medicine in Ireland and has previously served as Biomaterials Topic Chair for the Orthopaedic Research Society, as an EU Council Member of Tissue Engineering and Regenerative Medicine International Society (TERMIS) and a member of Irish Medicines Board Advisory Committee on Medical Devices. He is patented a number of technologies from his lab and has translated 2 technologies for bone and cartilage repair to the clinic. In addition he has served as an editorial board member for 9 leading journals. He was co-chair of the World Congress of Biomechanics which brought over 4000 delegates to Ireland in 2018. He has presented over 100 invited talks including keynotes at leading international conferences and symposia including the International Bone-Tissue Engineering Congress (Bone-TEC), Gordon Musculoskeletal Conference, World Congress of Biomechanics, TERMIS Annual meetings, World Conference on Regenerative Medicine, International Controlled Release Society, and Anatomical Society meetings. He has served as an invited reviewer for more than 100 scientific journals and as a grant reviewer and committee panelist for funding agencies worldwide.