Researcher (s):	Prof Nicholas Dunne (PI) Co-Researcher: Prof Helen McCarthy
Research Institution:	Dublin City University
Project Title:	A nanoparticle-loaded hydrogel for Epidermolysis Bullosa (reGENErate)
Research Area:	Gene Therapy
Start Date: Jan 2023	End Date: Jan 2025
Funded by:	DEBRA Ireland and the Irish Research Council

Lay Summary

Epidermolysis Bullosa (EB) is a group of genetic skin conditions that cause the skin and mucous membranes to blister, and is characterised by fragile skin and in some cases, internal organs and linings can be affected. Current treatments for people suffering from EB do not address the underlying cause of the condition, namely the genetic mutations that have been identified. From the outset, ReGENErate will attempt to address the cause of the EB condition by increasing levels of collagen VII and additionally, ensure that our proposed treatment can be manufactured at scale, be cost effective, remain stable at room temperature and most importantly can be applied by the patient themselves on their skin directly. ReGENErate is a locally applicable gel that is loaded with nanoparticles (nanogel) designed to increase expression of collagen VII.

The nanoparticles will contain genetic cargo encoding collagen VII and a natural amino acid peptide that functions to deliver the cargo into the skin cells where the collagen VII protein will be made.

The specific aims of this project are to: (i) create the gel and ensure functionality of our nanoparticles to increase collagen VII, (ii) assess and validate our nanogel using *in vivo* models that have no collagen VII, (iii) confirm the safety of the nanogel *in vivo* with repeated application and (iv) develop a patented formulation, application and manufacturing plan that aligns with clinicians and patient's needs. Specific outputs will include technological evidence of a functional nanogel than can be applied to the wounds of EB along with commercial exploitation and route to clinical translation roadmaps of how this can be developed into an actual product termed "ReGENErate".

Additionally, through a planned PPI programme, we will ensure the research is conducted with the full participation of EB patients, family members and carer community.

Project Abstract

Epidermolysis Bullosa (EB) is a debilitating group of medical conditions, where a weak interface between the dermis and epidermis leaves the skin prone to delamination and blistering. Although almost 20 different genetic deformities have been shown to underlie 30 different variants of EB, the principal cause in the majority of patients is a deficiency in collagen VII expression. Collagen VII forms a vital component of the anchor ring fibrils that link the basement membrane of the dermis to the epidermis and an insufficiency in the expression of this molecule, caused by mutation in the Coll7A1 gene is what compromises the strength of the interface between these tissue layers. The localised reversal of EB is currently limited by low transfection efficiency and the significant challenge of delivering the requisite genetic material deep into the skin, which has structural modifications that inhibit the penetration of all but the smallest molecules.

Our solution is to deliver genetic cargo encoding collagen VII. The genetic cargo to be compared includes:

(i) mRNA with obvious benefits of direct translation to the functional protein, reduced risk of genomic integration but requires more frequent administration and

(ii) CRISPR that will result in long term overexpression but also has risks associated with genetic editing. In order to deliver the cargo inside the cells, we will use the a peptide (RALA) that will condense the genetic cargo into nanoparticles. We will create a nanogel system that contains the RALA/Collagen VII nanoparticles. The polymer-based nanogel is a water biodegradable and biocompatible “smart” material sensitive to the changes of the wound environment. With significant inputs from clinicians and patients, the proposed development of this medical device in this project will be manufactured via an environmentally friendly synthesis route at room temperature, which will be cost-effective and readily scalable.

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’

The DEBRA charity was founded in Ireland in 1988 to support patients and families living epidermolysis bullosa (EB). There are currently 300 people in Ireland with EB and

there are three key aims of the charity: (i) provide care, (ii) find a cure and (iii) fight the cause. It is the 2nd main aim that this project aligns with, specifically through research. It has been well documented that collagen VII is lacking in patients with EB, the problem has always been that the therapy required, however DNA or mRNA has been impossible to deliver without further exacerbation and irritation of the skin. The delivery system that Professors Dunne and McCarthy plan to use to deliver collagen VII inside the skin cells is composed of natural amino acids and does not evoke a negative response. Within the 2nd aim there are key strategic objectives to:

(i) fund more research into EB therapies which this call does,
(ii) translate global research into improved clinical care and
(iii) bring more researchers into EB research.

Prof Dunne, Prof McCarthy and our collaborator Prof Grover have +20-year track-record of developing and validating Biopharma/MedTech technology, which has been successfully translated to industry and commercialised for clinical use. Dunne and McCarthy are planning to apply our technologies as new researchers to EB. However, this project is significantly de-risked because we have expertise in gel formulation, genetic delivery and product development, all of which will result in clinical progression.

It is critical to note, that this will not be done in isolation as EB patients, family members, community carers and clinicians will be key stakeholders in helping us understand what works for them product-wise and what their needs are. Therefore, the planned PPI programme is pivotal to ensure public and patient involvement in the project is truly embedded in the project.

Quotes we have from Researchers

None

Researcher (s) Bio

Professor Nicholas Dunne is the Chair of Mechanical and Manufacturing Engineering in the School of Mechanical and Manufacturing, the Founding Executive Director of Biodesign Europe and the Executive Director of the Medical Engineering Research Centre Engineering (MedEng) at DCU. Professor Dunne is also a Visiting Research Professor of Biomaterials Engineering at the School of Pharmacy at the Queen's University of Belfast (QUB), an Adjunct Professor of the School of Mechanical Engineering at Trinity College Dublin and a Principal Investigator in the Trinity Centre for Bioengineering.

Prior to his appointment at DCU, he was the Professor of Biomaterials Engineering at QUB He has also held Joint-Directorship positions in the Advanced Materials and Processes Research Cluster and the Polymer Processing Research Centre at QUB.

Professor Dunne's research programme lies at the interface of materials science, engineering and biology. He leads a multidisciplinary group working at the host/biomaterial interface that has played a leading role in the development of biomaterials that simulate an efficacious drug delivery or therapeutic response. This work spans fundamental mechanisms at the host/material interface as well as translational research to target non-union bone defects, bone metastases and chronic wounds. This research has been developed via a strong, interdisciplinary programme complemented with over-arching institutional and industrial collaborations.

Internationally he is recognised as an authority on biomaterials for orthopaedic applications, having been awarded an Orthopaedic Research Society/British Orthopaedic Research Society Fellowship (2008) and the RAEng/Leverhulme Trust Senior Research Fellow Award (2010). His work has been supported continuously by RCUK, EU and Charity funding organisations and also attracts significant interest from industrial partners. To date, he has secured ≈€18.50M PI research funding (and €17.5M as CI) - from funders including EPSRC, MRC, Innovate UK, SFI, The Royal Academy of Engineering and several major multinational medical device companies.

He has authored +225 peer-reviewed journal publications and delivered +400 research presentations at national and international biomaterials and biomechanics conferences He is a Journal Editor of Biomaterials Advances and Editorial Board Member of Regenerative Biomaterials, Royal Society of Chemistry - Biomaterials Science, Journal of Materials Science: Materials in Medicine, International Journal of Biomaterials and Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine.

He is also highly passionate about engaging new and young researchers on matters that are important to their research career and professional development. This enthusiasm and motivation have been hardened during his time as President of Northern Ireland Bioengineering Society (2008-2015) and Spokesperson of the Young Scientist Fora of the European Society for Biomaterials (2010-2014) and UK Society for Biomaterials (2011-2015). He was the VP and Secretary of the Executive Organising Committee of the 11th World Biomaterials Congress (Glasgow, 2020) and also on the Executive Organising Committee member of the 8th World Biomechanics Congress

(Dublin, 2018). He is currently the Council Secretary of the European Society for Biomaterials and the President of the Royal Academy of Medicine in Ireland – Section of Bioengineering.