Researcher (s):	Prof Gareth Inman (PI) Co-Researcher: Prof Karen Blyth
Research Institution:	CRUK Beatson Institute, UK
Project Title:	Drug re-purposing for the treatment of RDEB squamous cell carcinoma
Research Area:	Drug Re-purposing
Start Date: Mar 2023	End Date: Mar 2025
Funded by:	DEBRA Ireland and UK

Lay Summary

RDEB patients frequently develop early onset multiple aggressive skin tumours (cSCC) which in nearly all cases have lethal consequences. A detailed understanding of RDEB cSCC remains elusive and there are no effective treatments or approved targeted therapies. There is an urgent need to rapidly identify therapeutics for RDEB cSCC and to rigorously evaluate them in stringent relevant pre-clinical models prior to testing in patients in clinical trials.

Investigation of the molecular basis of RDEB cSCC development and progression will continue to inform novel target identification. The process from target identification to drug development, preclinical testing, dose, scheduling, safety and toxicity testing and then clinical implementation can take many years and be prohibitively costly particularly in the rare disease setting where the patient population is relatively small.

The potential of drug re-purposing of drugs already clinically approved for safe use in patients with established dose and scheduling regimens holds exciting potential for EB patients. Here we will undertake an unbiased drug re-purposing screen of over 3,000 FDA approved drugs. We will develop and enhance an RDEB cSCC specific pre-clinical pipeline to stringently evaluate the potential of these drugs whilst also increasing our understanding of the pathogenesis of RDEB cSCC during this process.

At the completion of these studies we will have identified and taken 2 drugs all the way through our pipeline which will provide compelling evidence for their rapid deployment in clinical trials in RDEB patients for treatment of the ultimately lethal cancer complication of this devastating disease.

Project Abstract

Recessive Dystrophic Epidermis Bullosa (RDEB) is caused by inherited mutations in the COL7A1 gene that encodes type VII collagen (C7), the principal component of anchoring fibrils that are required for the structural integrity of the epidermal-junction in the skin. RDEB patients suffer from severe skin fragility, persistent skin blistering and wounding and have an exceptionally high risk of developing early-onset, aggressive and ultimately lethal cutaneous squamous cell carcinoma (cSCC). RDEB cSCC develops in a permissive environment of chronic inflammation, wound healing and fibrosis facilitated in part by cancer associated fibroblasts (CAFs). There is currently an incomplete understanding of the pathogenesis of RDEB cSCC and no currently clinically approved targeted treatment therapies. Here we will undertake a drug re-purposing screen of over 3,000 drugs already approved for use in patients with other disease conditions. We will develop and refine a stringent step-wise pre-clinical pipeline designed to assess the efficacy of drugs for inhibiting RDEB cSCC tumour cell survival both in-vitro and in-vivo; important indicators of therapeutic use. We will reveal the importance of CAFs in tumourigenesis and drug response and we will identify 2 drugs which show efficacy all the way through our pipeline. This process will circumvent the prohibitively time consuming and costly process of drug development and safety testing and will provide compelling evidence for the rapid and safe deployment of these 2 drugs in patients in clinical trials for RDEB cSCC therapy.

Blog post written about project for website

None

Quotes we have from Researchers

None

Researcher (s) Bio

None