Researcher (s):	Prof Andrew South (PI) (on behalf of Prof Rodeck on his passing) Dr Alexander Nystrom (Co-researcher)
Research Institution:	Jefferson Medical College, Philadelphia, USA and University of Freiburg, Germany
Project Title:	Multimodality targeting of chronic inflammation and fibrosis in epidermolysis bullosa
Research Area:	Wound Healing
Start Date: Jan 2021	End Date: Jan 2024
Funded by:	DEBRA Ireland and Austria

Lay Summary

This project aims to examine whether combinations of 3 different drugs (losartan, trametinib and RTA408) can have synergistic effects in reducing inflammation and fibrosis (scarring) in two mouse models of EB for potential development for use clinically.

The study will investigate improved outcomes compared to the use of single drugs and reduced toxicity if lower doses of individual drugs are sufficient when used in combination. Losartan and trametinib are already FDA approved and used in clinical practice for other indications, and RTA408 is currently in clinical development for use in other indications.

Project Abstract

This application seeks to explore whether three different small molecule agents with anti-inflammatory and/or anti-fibrotic activity can be combined to improve symptom management of blistering genodermatoses including RDEB. The three participating laboratories have developed evidence for single modality activity for each of these agents (losartan, trametinib, RTA408) in fibrotic diseases including genetic models of EB.

These are (1) the collagen VII hypomorphic RDEB model used by Dr. Nyström to demonstrate efficacy of losartan in delaying fibrosis development and (2) the non-Herlitz junctional EB (LambC2jeb) model developed originally by Dr. Sundberg and used by Dr. Rodeck to demonstrate efficacy of the synthetic triterpenoid RTA408 in alleviating disease severity. Our approach is based on the hypothesis that co-

targeting different molecular mediators of inflammation and fibrosis (inflammasome/IL-1beta, MEK, AT1R) improves efficacy of pharmacological intervention. For proof-of-concept we will conduct efficacy testing of dual and triple drug combinations in two consecutive phases.

Phase 1 testing will be done in LambC2jeb mice because the phenotype is less severe with late onset in adult mice. This facilitates drug administration and monitoring of drug effects over time.

Superior drug combinations preselected in LambC2jeb mice will be tested in Phase 2 using collagen VII hypomorphic mice in which local blistering is induced. This strategy facilitates monitoring therapeutic effects when using different routes of administration (topical vs. systemic). An important aspect of these studies is to test whether combining these agents enables lower dosing thus reducing adverse events. Further clinical development of the combination producing superior effects in the animal models is envisioned.

Blog post written about project for website

None

Quotes we have from researchers

“This project, original conceived by the late Professor Ulrich Rodeck, is looking at three different drugs, each with a separate mode of action but all targeting the same problem – the inflammation and fibrosis that drives many of the symptoms of EB. Our hope is that together these three drugs will be better than one drug on its own and our research will provide a blueprint for future clinical trials.” – Prof Andrew South

“The use of drug combinations are becoming increasingly important for the treatment of complex diseases such as those where inflammation and fibrosis are prevalent. Here we are looking at combinations of three drugs, each with a proven track record in the laboratory, with the aim of finding a “sweet spot” for treating patients with EB.” – Dr Alexander Nystrom

Researcher (s) Bio

Prof Andrew South is a professor at Thomas Jefferson University, Philadelphia, USA. His laboratory focuses primarily on cutaneous SCC (cSCC) which is the most frequent skin cancer with malignant potential and contributes to greater than 1 in 4 skin cancer deaths in Caucasian populations. Patient groups with a high propensity to develop these tumors face a significant risk of mortality. One such group is the genetic skin

blistering condition recessive dystrophic epidermolysis bullosa (RDEB). His laboratory has a long standing interest in trying to understand why mutations in the single COL7A1 gene lead to frequent and multiple life-threatening skin cancers.

Dr Alexander Nystrom is a group leader in the Department of Dermatology, Medical Centre at the University of Freiburg, Germany. His research group's translational research is focused on dissecting the roles of the extracellular matrix in skin during homeostasis, normal and pathological wound healing, immune surveillance and in cancer. They use this knowledge to develop new therapy approaches for treatment of bacterial infections, fibrosis and squamous cell carcinoma. A specific interest is on improving the understanding of disease mechanisms in the genetic skin blistering disease, dystrophic epidermolysis bullosa, toward developing safe, efficacious targeted-treatment.