Preventing skin toxicities induced by EGFR inhibitors by topically blocking drug-receptor interaction

Sharon Merims[1,3], Lyora Aharonov[3] , Liza Weinstein[1,3], Nethanel Friedman[2,3], Ofra Benny[2,3]

Sharett Institute of Oncology, Hadassah Medical Center, Hebrew University of Jerusalem[1],

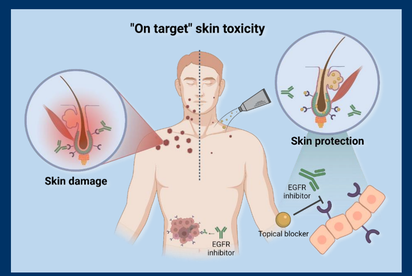
Institute for Drug Research, School of Pharmacy, Faculty of Medicine, Hebrew University of Jerusalem[2], EMRIS pharma Ltd.[3]

ABSTRACT

Epidermal growth factor receptor inhibitors (EGFRi) are commonly used in cancer treatment but often induce severe skin toxicities, impacting patients' quality of life and compromising therapy. Treatment protocols for skin toxicities caused by EGFRi are of limited benefit, and the need for new skin-directed treatments remains unmet.

We developed a novel approach to manage "on-target" skin toxicity by locally blocking the drug's effects at the site of toxicity without reducing the systemic dose to the tumor. We identified a promising small molecule, SDT-011, which blocks the binding of EGFR inhibitors cetuximab and panitumumab to EGFR and reactivates EGFR signaling in keratinocytes. We have successfully developed a topical formulation of SDT-011 that penetrates deep skin layers and hair follicles. Our novel approach has the potential to significantly reduce skin toxicity associated with EGFR inhibitors.

Graphical ABSTRACT



INTRODUCTION

The field of personalized medicine and targeted therapies has led to specific 'on-target' toxicities, affecting tissues that highly express the same molecular target as the tumor. Epidermal growth factor receptor inhibitors (EGFRi) cause severe skin toxicity, with the most common reaction being a papulopustular eruption, an acne-like rash (Fig1). These lesions cause many patients to withhold or reduce treatment (1). Current treatment strategies for treating these skin toxicities focus on symptom reduction rather than preventing the initial trigger that causes the toxicity and are of limited benefit (2). There is an urgent need for new potent approaches to treat these toxicities. In this study, we developed a compound and method for preventing 'on target' skin toxicity by topically blocking drug-receptor interaction at the site of toxicity without reducing the systemic dose reaching the tumor.

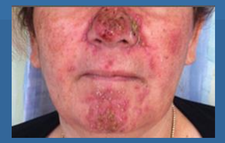
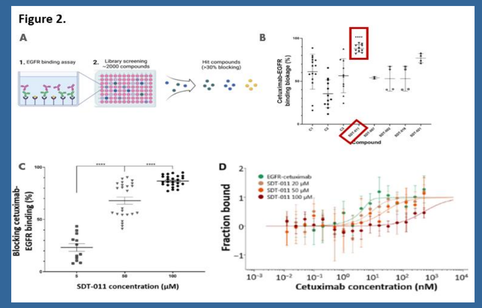


Figure 1. Cetuximab induced papulopustular rash.

PROOF OF CONCEPT

Blocking EGFRi monoclonal antibodies binding to EGFR

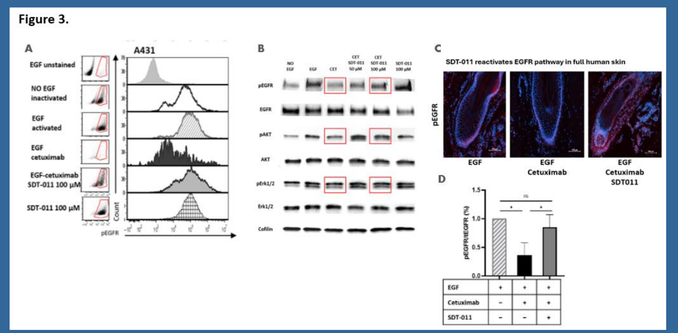
Figure 2. A) Illustration of the process used to identify lead compounds. “Hit” molecules were identified by screening a 2000 small molecule drug-like library (DIVERSet-EXP, Chembridge). B) SDT-011 consistently inhibited more than 80% of EGFR-cetuximab binding, as measured by enzyme-linked immunosorbent assay (ELISA) C) SDT-011 blocks cetuximab binding to hEGFR in a dose depended manner. (n = 12, 24, and 25, respectively) D) Dose-response blocking of cetuximab-EGFR binding by SDT-011 measured by microscale thermophoretic analysis (Kd values of 12.7 and 478.9 nM, respectively, n = 5 per tested concentration).



PROOF OF CONCEPT cont.

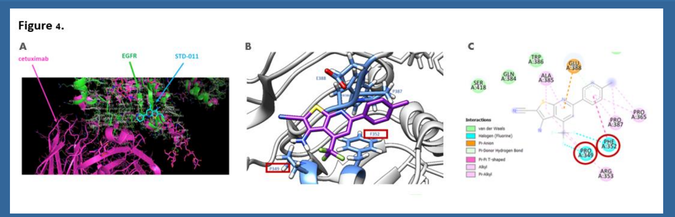
SDT-011 blocks cetuximab’s inhibition and reactivates EGFR pathway

Phospho-EGFR flow cytometry analysis of A431 (A) cells. The cell lines were treated with cetuximab and SDT-011 and stimulated with EGF (180 ng/ml) for 20 min and stained with phospho-EGFR antibody (pEGFR) (n = 3, one-way ANOVA analysis). (B) Western blotting analysis demonstrating SDT-011's effect on EGFR downstream phosphorylation in HaCat cells. (C) Phospho-EGFR measurement in whole human skin samples. The skin samples were incubated with EGF in DMEM over 48 hours. Immunofluorescence microscopy (×20) demonstrates epidermis and hair follicle structure using DAPI staining (blue). Total EGFR and pEGFR are shown in red. Scale bars, 100 μm. (D) Quantification of pEGFR activation in whole human skin analyzed by immunofluorescence.



Mechanism of action:

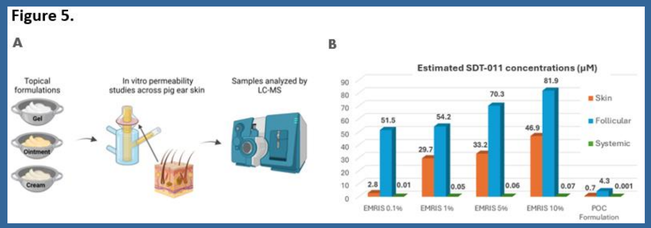
SDT-011 interacts with the same residues on EGFR found to be critical for cetuximab and panitumumab binding (residues PRO349, PHE352, PRO387) (4) Figure 4: (A) Using in silico modeling SDT-011 binding site was identified. (B) SDT-011 interacting with EGFR amino acids previously reported to be crucial to cetuximab binding (key amino acids highlighted in blue). (C) Two-dimensional ligand-protein interaction diagram of SDT-011 with amino acids of EGFR. Figures generated using UCSF Chimera and Discovery Studio.



DRUG DEVELOPMENT

Drug development – EMRIS pharma

In 2023, EMRIS Pharma was established to create a topical formulation of SDT-011 aimed at treating EGFRi-induced skin toxicity. (A) Illustration of the process: developing the formulation developed by EMRIS Pharma effectively targets and concentrates SDT-011 in hair follicles, where EGFRi commonly causes acneiform rashes. (B) FRANZ assays in vitro permeability studies using pig ear skin demonstrate that SDT-011 concentrates in hair follicles and skin with minimal systemic penetration.



CONCLUSIONS

Our innovative approach aims to ***prevent*** skin toxicities caused by EGFRi monoclonal antibodies by blocking the initial trigger causing skin damage. This new intervention has the potential to revolutionize the management of skin toxicities, leading to improved treatment outcomes and a better quality of life for affected individuals.

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