SELECTED OPPORTUNITIES IN DERMATOLOGY

Use of NGAL Inhibitors for treating chronic wound (BIO 19230)

USE OF NGAL INHIBITORS FOR TREATING CHRONIC WOUND (BIO 19230)

Product factsheet

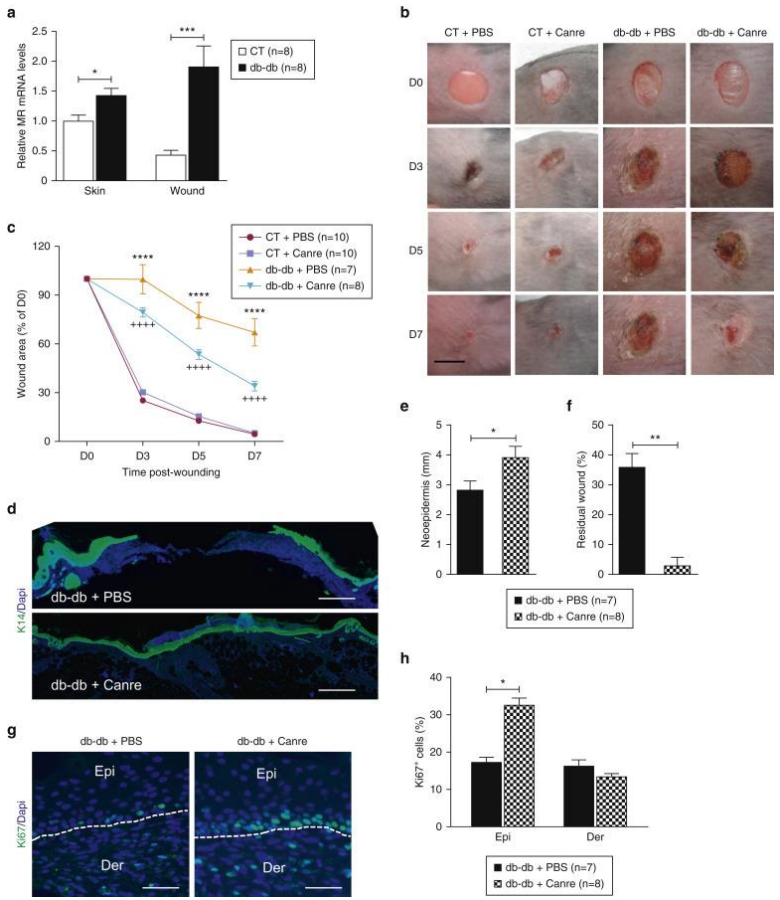
In Vivo PoC

- **Target:**
  - Lipocalin 2 (NGAL)
- **Product:**
  - Tested: KO mice
  - Could be generated: NGAL inhibitors for topical use
- **Application:**
  - Wound healing
- **Rational:**
  - Chronic wounds and in particular diabetic ulcers are a serious complication of diabetes. Unresolved inflammation, associated with the dysregulation of both the phenotype and function of macrophages, is involved in the poor healing of diabetic wounds
- **POC:**
  - Topical pharmacological inhibition of the mineralocorticoid receptor (MR) by canrenoate or MR siRNA can resolve inflammation to improve delayed skin wound healing in diabetic mouse models
  - Diabetic Lcn2-deficient mice showed improved wound healing, associated with macrophage M2 polarization and angiogenesis
  - Recombinant Lcn2 protein prevented IL4-induced macrophages switch from M1 to M2 phenotype
- **Patent and publication:**
  - EP19305664: USE OF NGAL INHIBITORS FOR THE TREATING CHRONIC WOUND
  - *Cutaneous Wound Healing in Diabetic Mice Is Improved by Topical Mineralocorticoid Receptor Blockade*. Nguyen VT *et al*. **J Invest Dermatol**. 2020 Jan;140(1):223-234.

USE OF NGAL INHIBITORS FOR TREATING CHRONIC WOUND (BIO 19230)

Proof of concept

Canrenoate improves delayed wound healing in type 2 diabetic mice

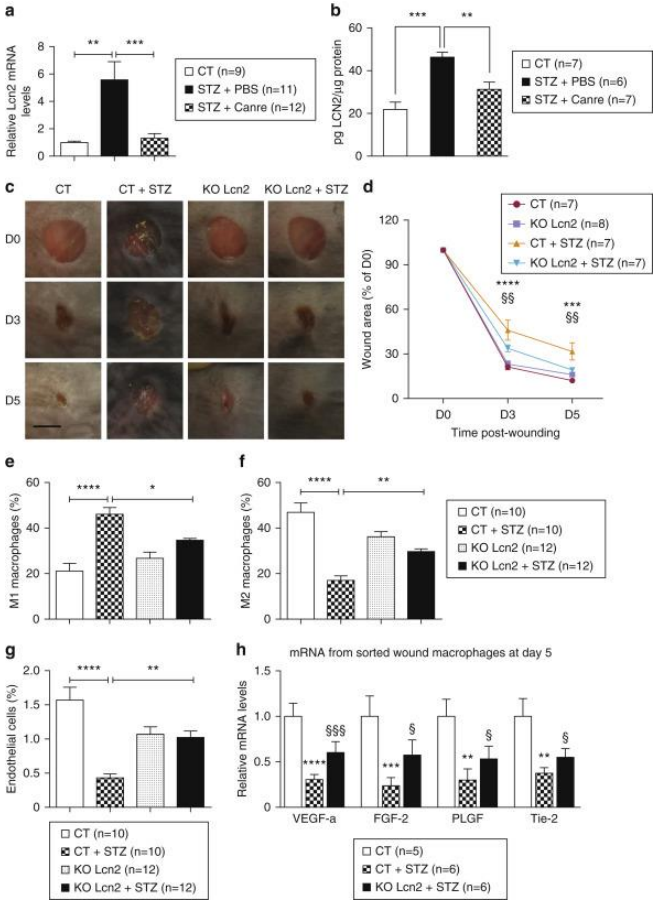


*(**a**) Real-time PCR analysis of MR mRNA expression in the skin or wounds (day 7) of db-db mice, relative to that of CT. (**b**) Photographs and (**c**) quantification of the wound area of CT and db-db mice treated with canrenoate or PBS at the indicated time post-wounding. (**d**) Wound sections at day 7 post-wounding labeled with anti-K14 antibody (green) and DAPI (blue). Quantification of (**e**) the length of the neoepidermis and (**f**) diameter of the residual wound. (**g**) Anti-Ki67 (green) staining and quantification of Ki67-positive cells in the neoepidermis and (**h**) underlying dermis; dotted lines represent the dermo-epidermis junction. Data represent mean ± SEM; n = number of mice per group, from 2 experimental series. (a, e, f, and h) Mann-Whitney test; c: two-way ANOVA followed by the Newman-Keuls multiple comparison test. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001 db-db vs CT; ++++P < 0.0001 db-db vs db-db + Canre. ANOVA, analysis of variance; Canre, canrenoate; CT, control; Der, dermis; Epi, neoepidermis; MR, mineralocorticoid receptor; PBS, phosphate buffered saline; SEM, standard error of the mean. (d) Bar = 500 µm, (g) Bar = 100 µm.*

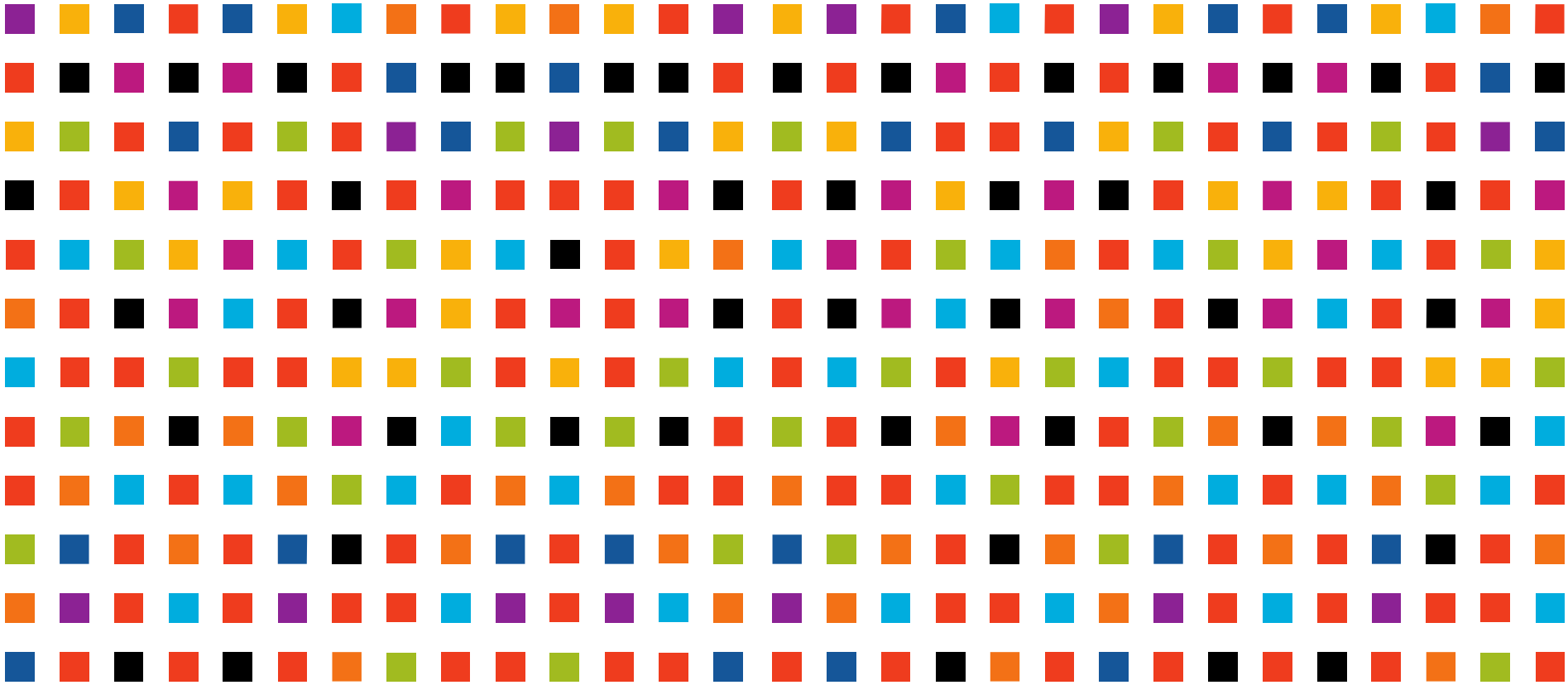
USE OF NGAL INHIBITORS FOR TREATING CHRONIC WOUND (BIO 19230)

Proof of concept

LCN2 deficiency prevents the diabetes-induced delay of wound healing



*(**a**) LCN2 mRNA and (**b**) protein levels in wounds at day 5 were analyzed by real-time PCR and ELISA. (**c–h**) Diabetes was induced in wild-type (CT) and Lcn2 KO mice by STZ injections before wounding. (**c**) Photographs and (**d**) quantification of the wound area from CT and Lcn2 KO mice with or without STZ treatment at the indicated times post-wounding. (**e**) M1 and (**f**) and M2 macrophages and (**g**) endothelial cells of wounds at day 5 were quantified by FACS analysis. (**h**) Total macrophages were sorted from wounded skin at day 5 and angiogenic factors mRNA levels were analyzed by real-time PCR. Data represent mean ± SEM; n = number of mice per group, from 2 experimental series. (a, e–h) one-way ANOVA followed by the Newman-Keuls multiple comparison test; (d) 2-way ANOVA followed by the Newman-Keuls multiple comparison test. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001 CT + STZ vs CT. §§P < 0.01 CT + STZ vs Lcn2 KO + STZ. ANOVA, analysis of variance; Canre, canrenoate; CT, control; FACS, fluorescence activated cell sorting; KO, knockout; PBS, phosphate buffered saline; SEM, standard error of the mean; STZ, streptozotocin.*



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