"Keratinocyte-Specific Progranulin Deficiency in psoriasiform or AD inflammation"

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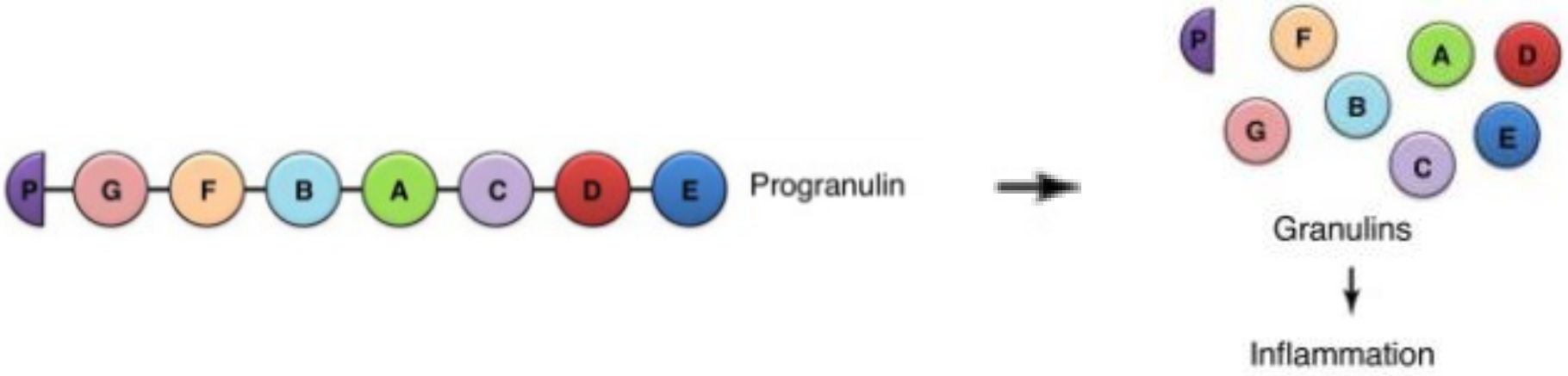
Regulation of T cell immunity &
Systemic immunity

Introduction 1. : Proganulin



Progranulin (PGRN), also known as **granulin precursor** or **GP88**, is a secreted glycoprotein encoded by the *GRN* gene on chromosome 17q21.
It consists of multiple granulin peptide domains.
PGRN functions as a multifunctional growth factor involved in **cell proliferation, tissue repair, inflammation regulation (mostly anti-inflammation), and other immune modulation**.

Introduction 2. Physiological Functions of Progranulin (PGRN)

Function	Description
Anti-inflammatory Action	PGRN binds directly to **TNF receptors (TNFR1 and TNFR2)**, thereby antagonizing **TNF-α signaling** and reducing inflammation.
Immune Regulation	Modulates macrophage and T-cell activation, balancing pro- and anti-inflammatory immune responses.
Tissue Regeneration	Promotes wound healing, fibroblast proliferation, and epithelial repair.
Neuroprotection	Supports neuronal survival and prevents neurodegeneration.

Introduction 3.

- Lysosomes play a pivotal role in inflammation, and progranulin (PGRN), a multifunctional growth factor, regulates lysosomal function and is associated with neutrophilic inflammation.
- PGRN has been implicated in inflammatory diseases, diabetes, and obesity-related adipokine regulation.
- Although PGRN is known to modulate immune responses, its specific role in keratinocytes during psoriasis (PsO) or atopic dermatitis (AD)-like inflammation remains unclear.

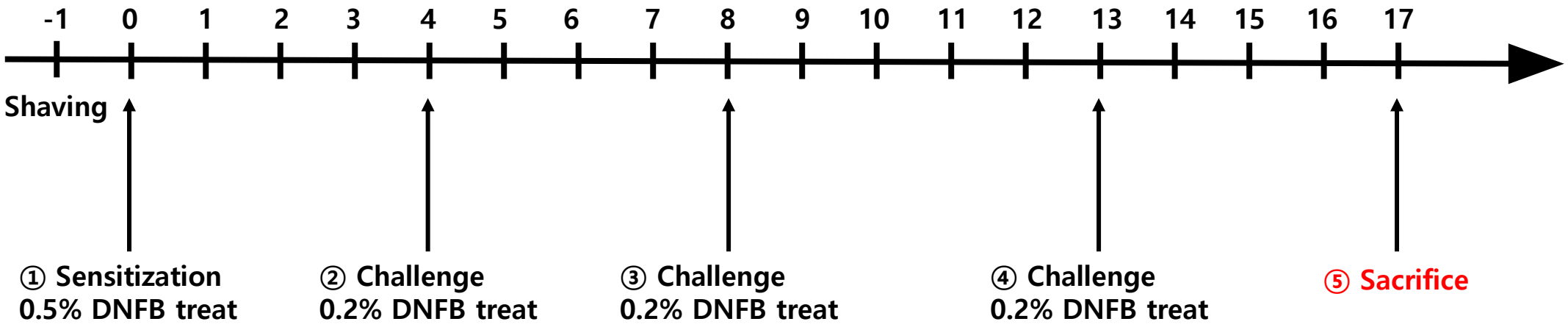
Objectives

- To investigate the function of keratinocyte-derived PGRN in Psoriasis and AD—both of which are commonly associated with diabetes and obesity as comorbidities
- To identify potential therapeutic targets focusing epidermal keratinocytes

Methods

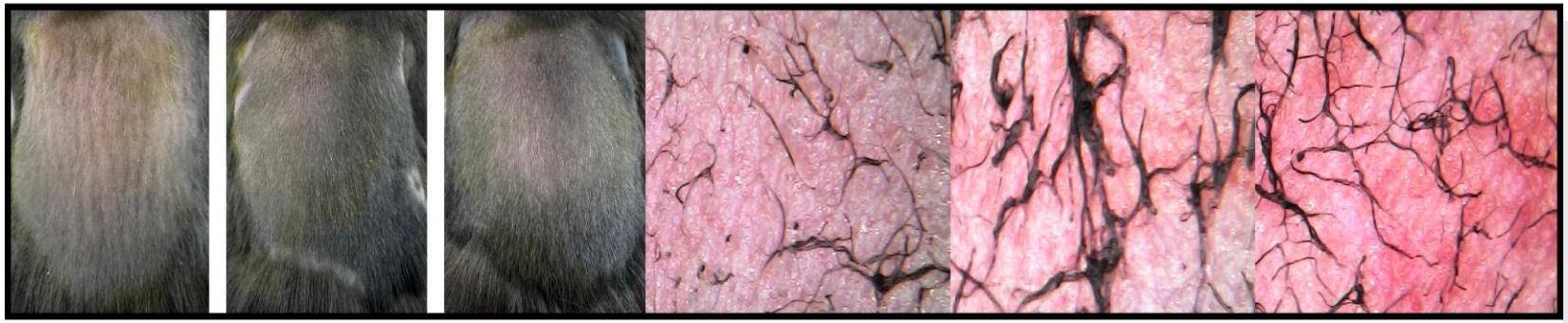
- We used Keratinocyte-specific PGRN knockout (KO) mice by crossing floxed PGRN mice with K14-Cre transgenic mice. Age- and sex-matched wild-type (WT) littermates were used as controls.
- Psoriasis or AD-like skin inflammation was induced by daily topical application of imiquimod (IMQ), DNFB, or MC903 (vitamin D3 analogue)
- Clinical severity was evaluated based on erythema, scaling, and skin thickness (induration or thickening).

1. Experimental Plan
DNFB treatment for AD-like dermatitis model

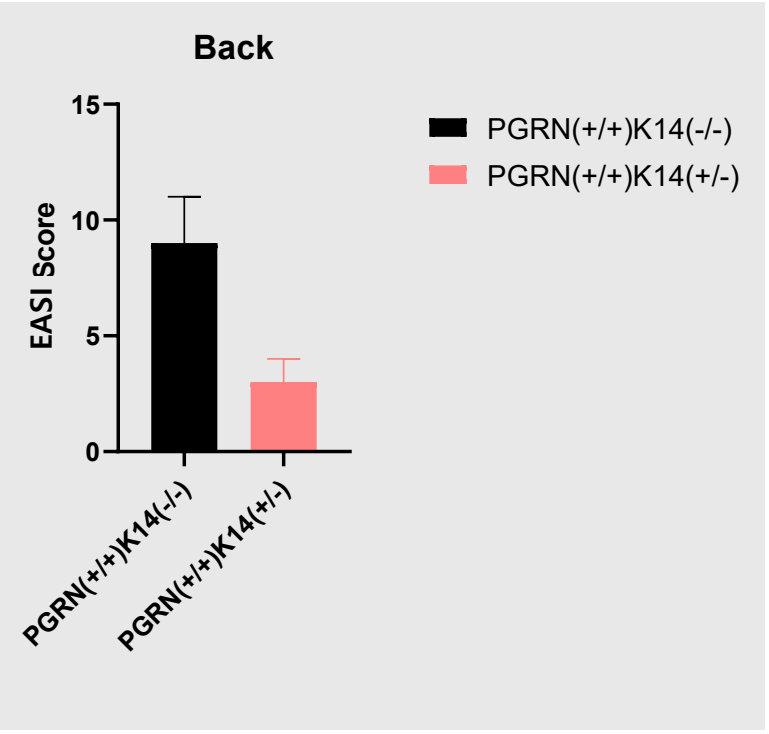


Results 1-1. Keratinocyte specific KO of progranulin reduces inflammation on mouse back skin

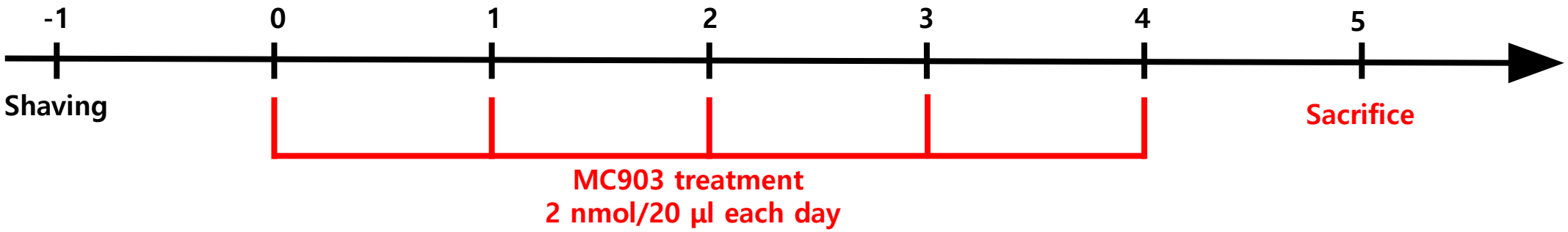
PGRN(+/+)-K14Cre(-/-) group



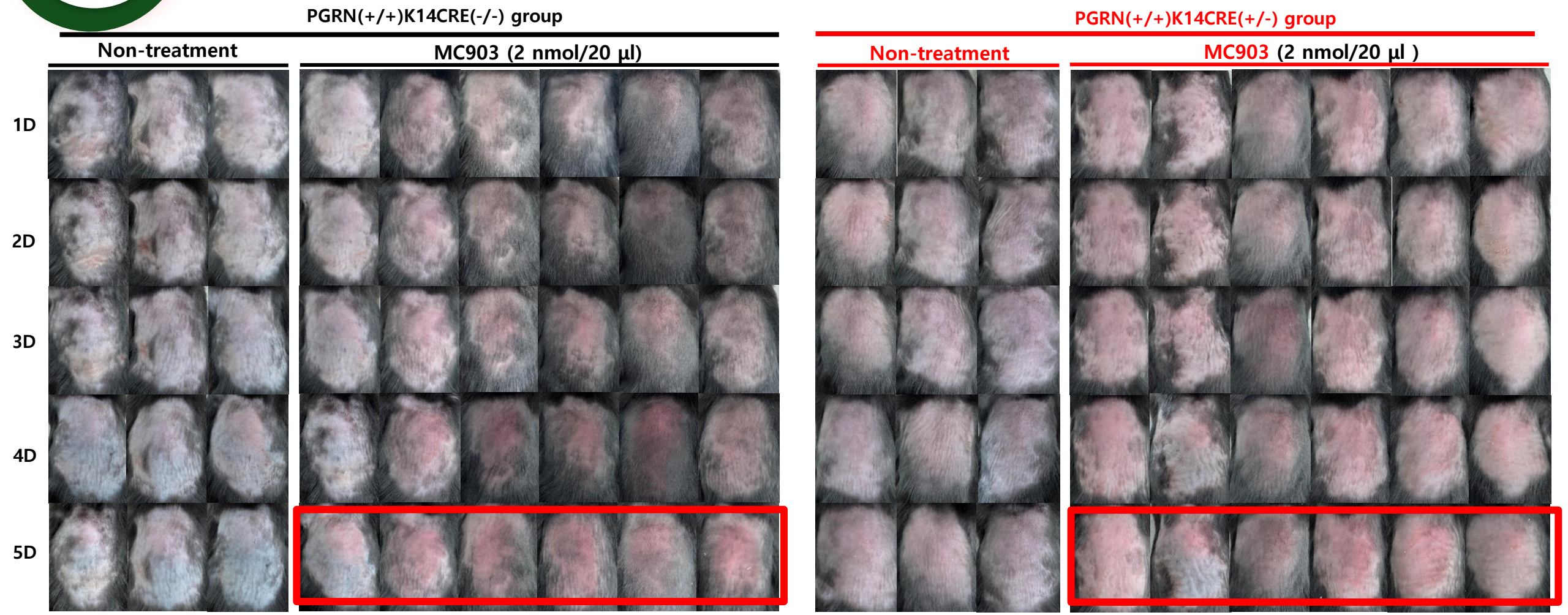
PGRNfl/fl-K14Cre+/- group



2. Experimental Plan
MC903 treatment for AD model

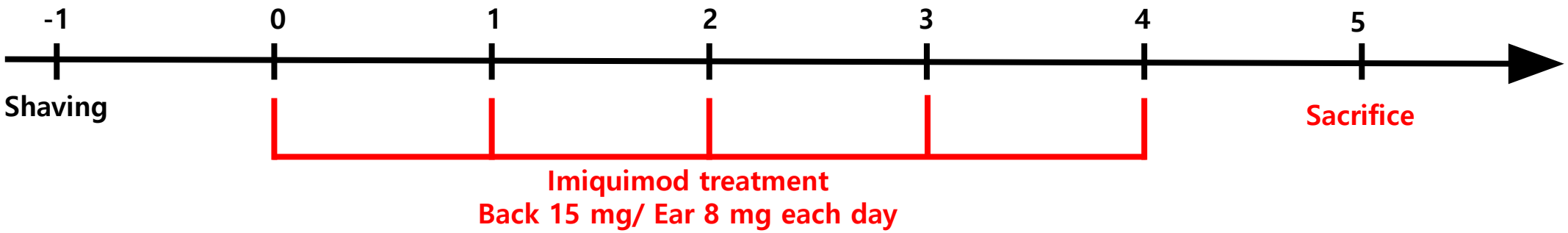


Result 2-1.


PGRN(+/+)K14CRE(-/-) group
Non-treatment
MC903 (2 nmol/20 μl)
PGRN(+/+)K14CRE(+/-) group
Non-treatment
MC903 (2 nmol/20 μl)
1D
2D
3D
4D
5D

3. Experimental Plan : Keratinocyte specific PGRN KO mouse Immiquimod for psoriasis model

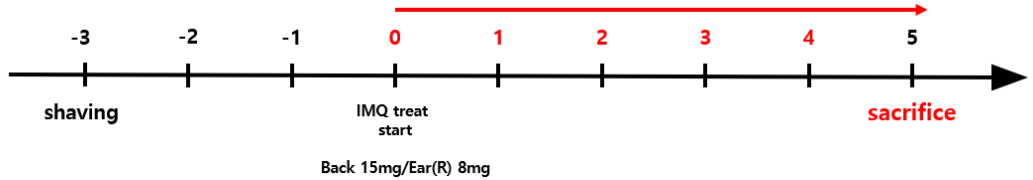
Use PGRNfl/fl-K14CreK14(-/-), PGRNfl/fl-K14Cre(+/-), Systemic PGRN KO
9 weeks-old female mice

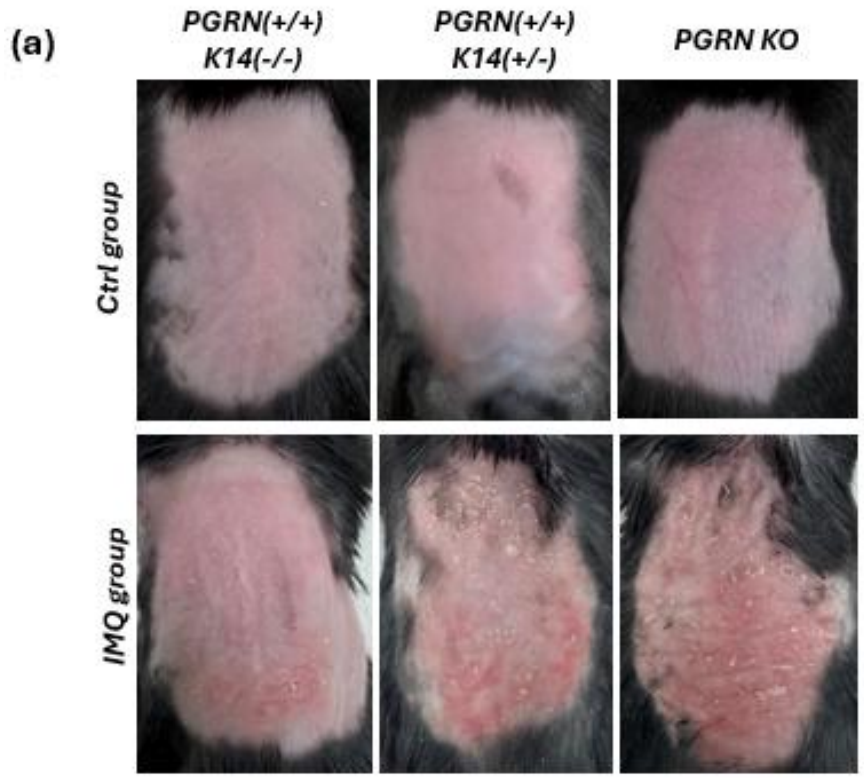


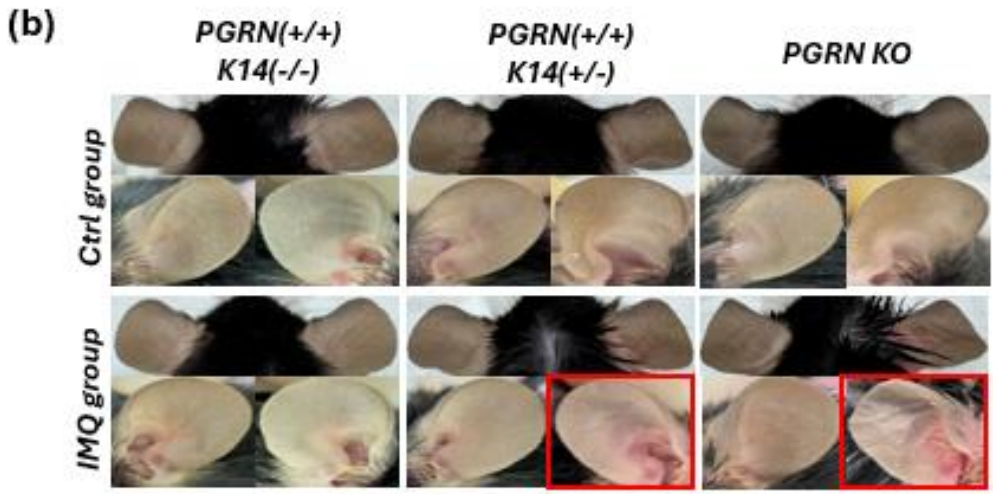
Results 3-1. skin psoriasiform inflammation

PGRNfl/fl-K14CreK14(-/-), PGRNfl/fl-K14Cre(+/-), Systemic PGRN KO
Imiquimod treatment

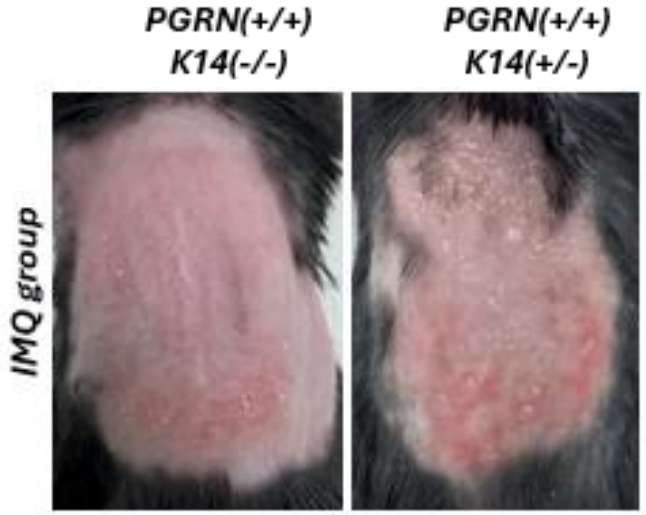
Back 15 mg , Ear(only right side) 8 mg treatment

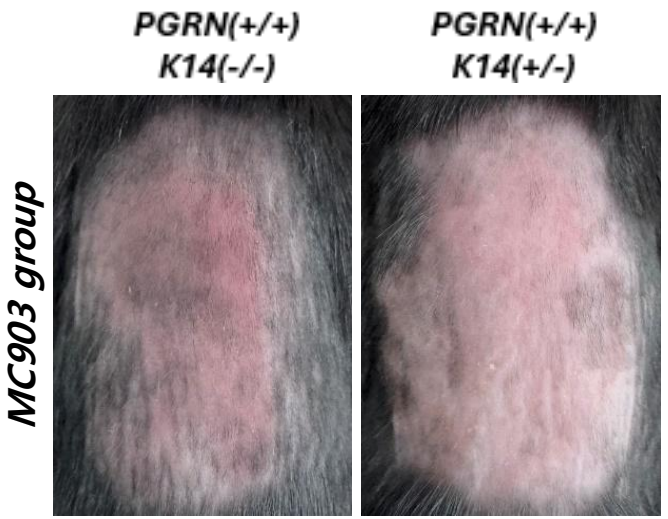


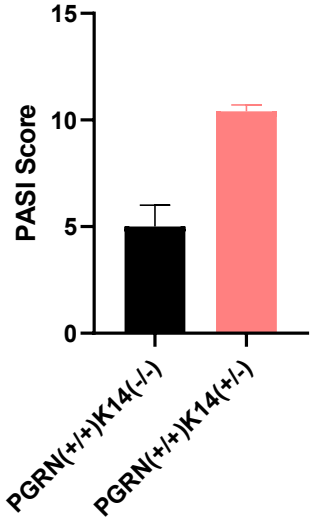


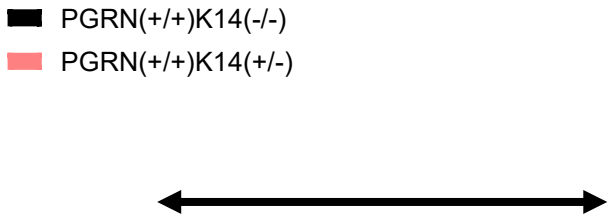


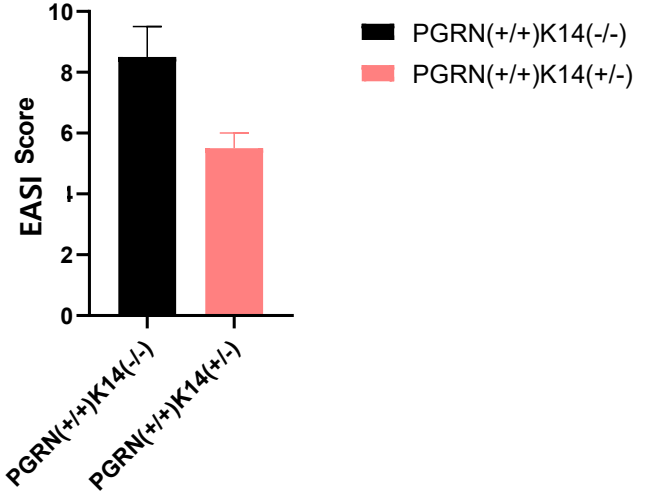
Discussion 1. From the summary of our results











The results are the opposite.

Discussion 2.
Progranulin prevents dementia by neuroprotection

- Psoriasis is related to neurologic disorders as comorbidities.
- GRN mutations cause progranulin haploinsufficiency, which eventually leads to frontotemporal dementia (FTD-GRN).
- PR006 is an investigational gene therapy delivering the granulin gene (*GRN*) using an adeno-associated virus serotype 9 (AAV9) vector.
- PR006 AAV-GRN offers a clear translation for GRN haploinsufficiency disorders, with demonstrable CSF PGRN increases in the clinic, but there were safety signals by gene therapy.

Progranulin AAV gene therapy for frontotemporal dementia: translational studies and phase 1/2 trial interim results. *Nat Med* **30**, 1406–1415 (2024)

Discussion 3. Role of PGRN in skin inflammatory disorders

- **Mechanism of Action: Unclear**
  - PGRN may bind to TNF receptors, blocking TNF-α signaling and suppressing NF-κB–mediated inflammation.
  - It may also regulate cytokine networks and lysosomal homeostasis.

- **PGRN in Skin Inflammation:**
  - PGRN is upregulated in psoriasis and atopic dermatitis.
    Imiquimod-induced psoriasiform dermatitis mouse demonstrate that recombinant PGRN attenuates epidermal hyperplasia and inflammatory cytokines such as IL-6, IL-17, and TNF-α.
  - These findings indicate that PGRN functions as an intrinsic anti-inflammatory mediator in the skin, and dysregulation of its expression or processing may contribute to chronic inflammatory skin conditions.

Conclusion

In psoriasis, progranulin acts as a protective factor that alleviates skin inflammation. Keratinocyte-derived progranulin functions as an anti-inflammatory mediator and a potential therapeutic target. Targeting keratinocyte-derived PGRN could offer a novel therapeutic approach for psoriasis and related immune diseases. The mechanism may be possibly through down-modulation of IL-17 related inflammation and antimicrobial peptides, as well as TNF-α–related cytokine pathways.

In contrast, in atopic dermatitis, progranulin may aggravate inflammation and combining with diet modulation should be further explored.

Although the mechanism should be further studied, keratinocyte derived progranulin may protect Th1 or Th17 pathway, not Th2 type inflammation.
As PGRN is associated with neutrophilic inflammation in general, further studies should be followed for it.

Acknowledgements

- This work was supported by the contributions of many colleagues.
- We would like to especially thank:
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Thank you