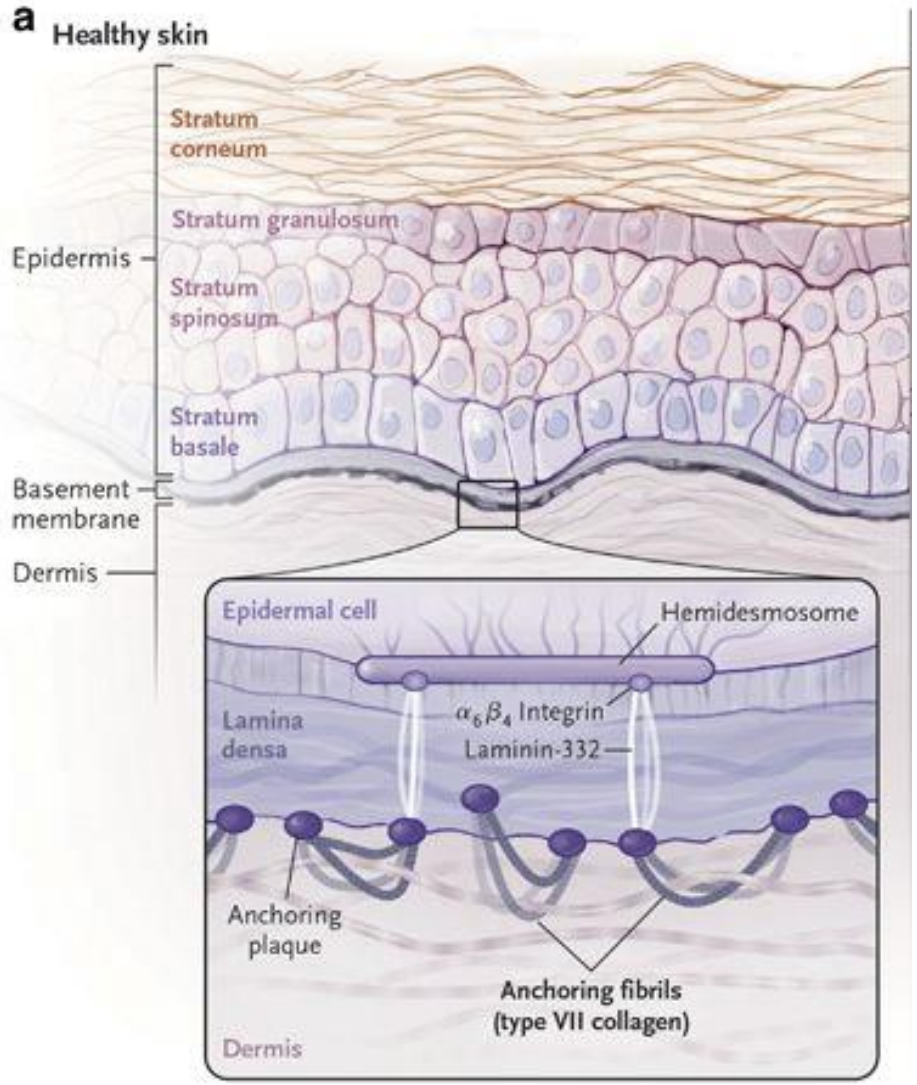
Waipapa Taumata Rau
University of Auckland

Developing a Gene therapy for fragile skin conditions like EB

22nd August 2025

Dr. Hilary Sheppard

What Causes EB?

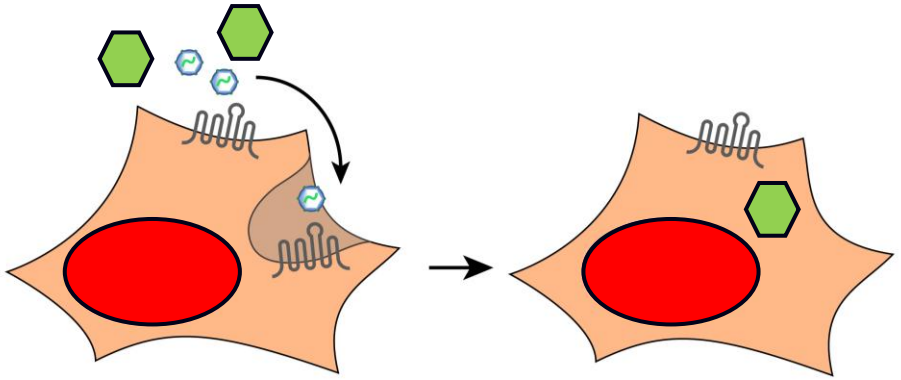


← EBS (keratin)

← JEB (laminin)

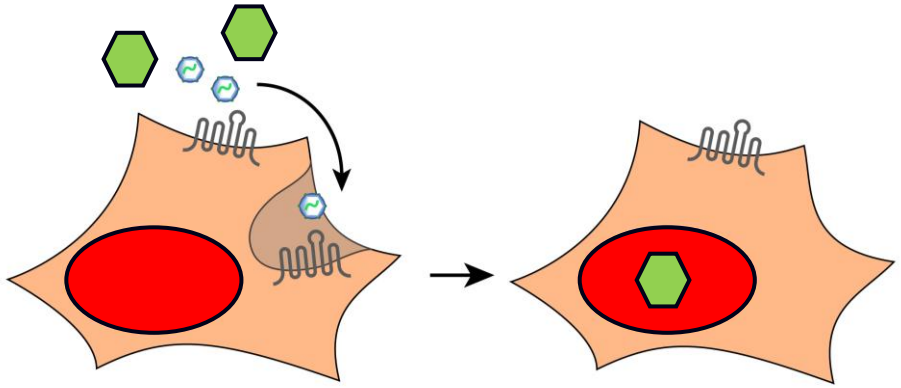
← RDEB (collagen 7)

Recent FDA approved therapies for RDEB



Vector does NOT integrate

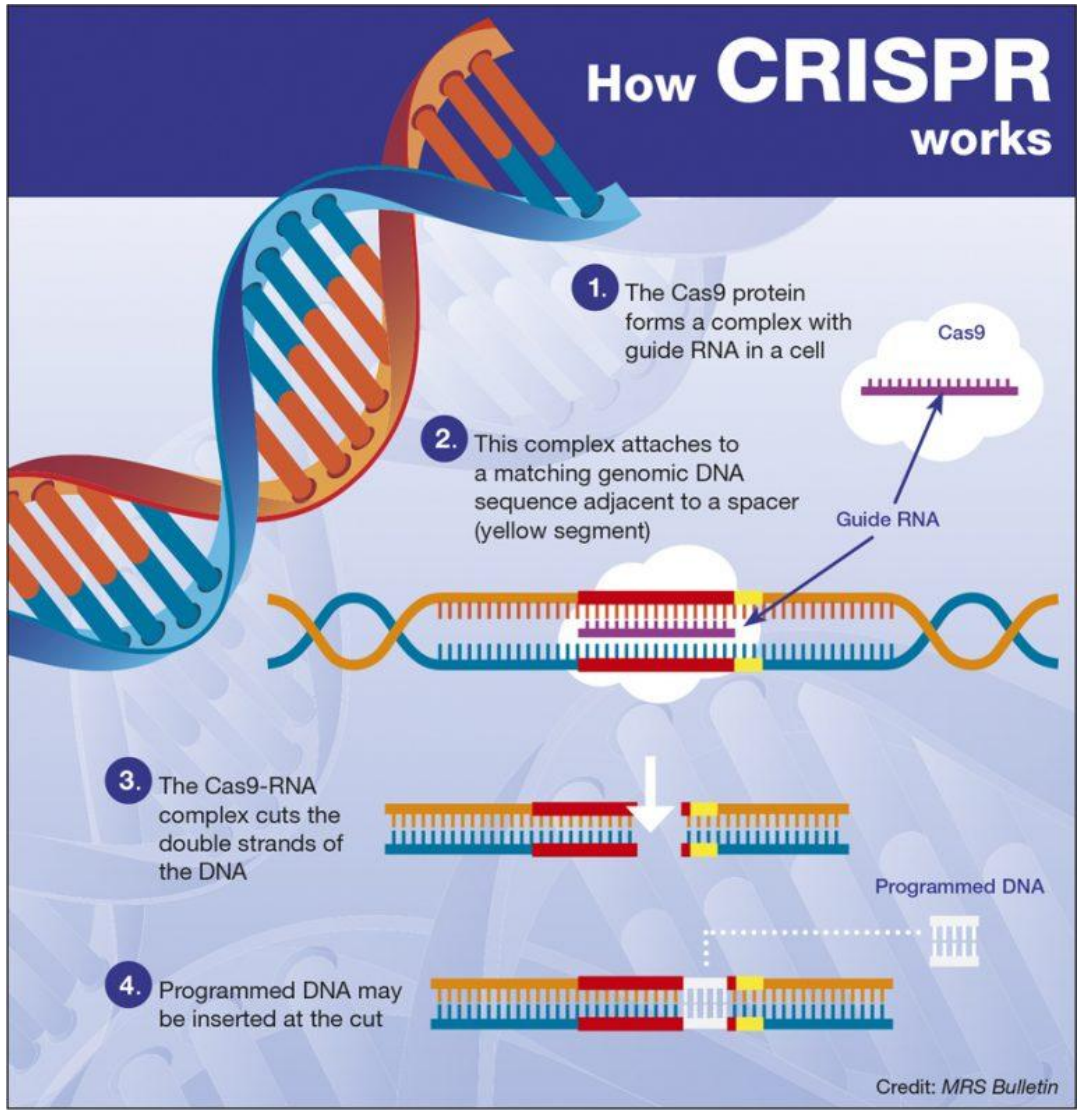
Vyjuvek – cream, delivers Col7 (temporary)

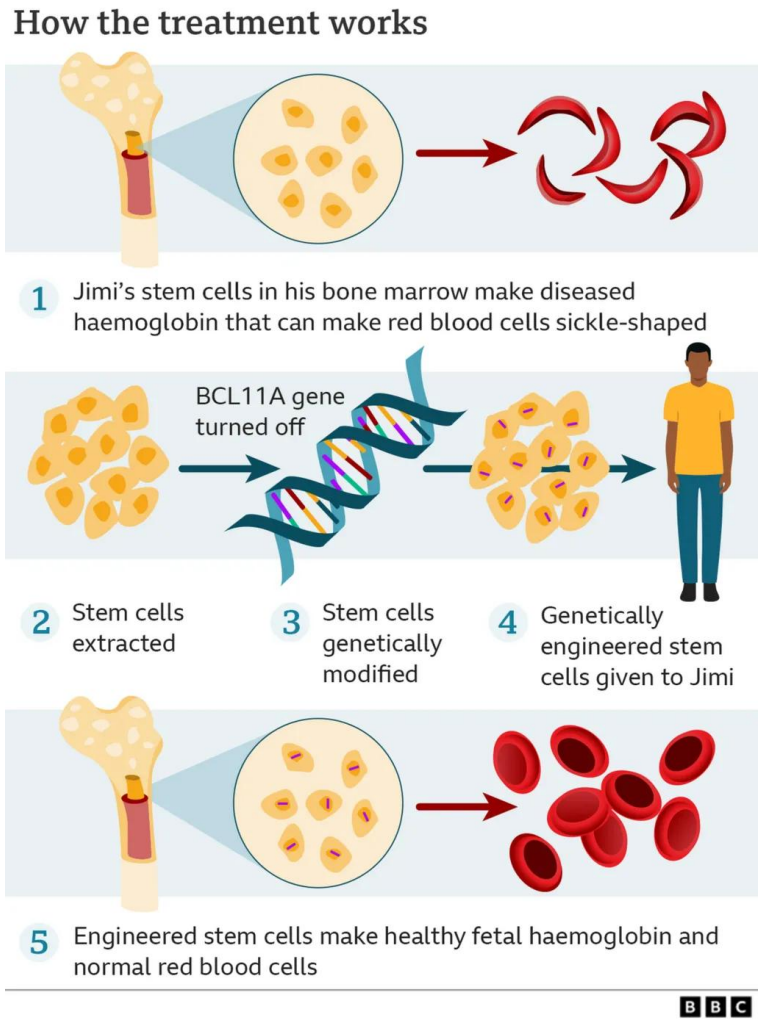


Vector DOES integrate

Zevaskyn – skin sheet, delivers Col7 (long lived)

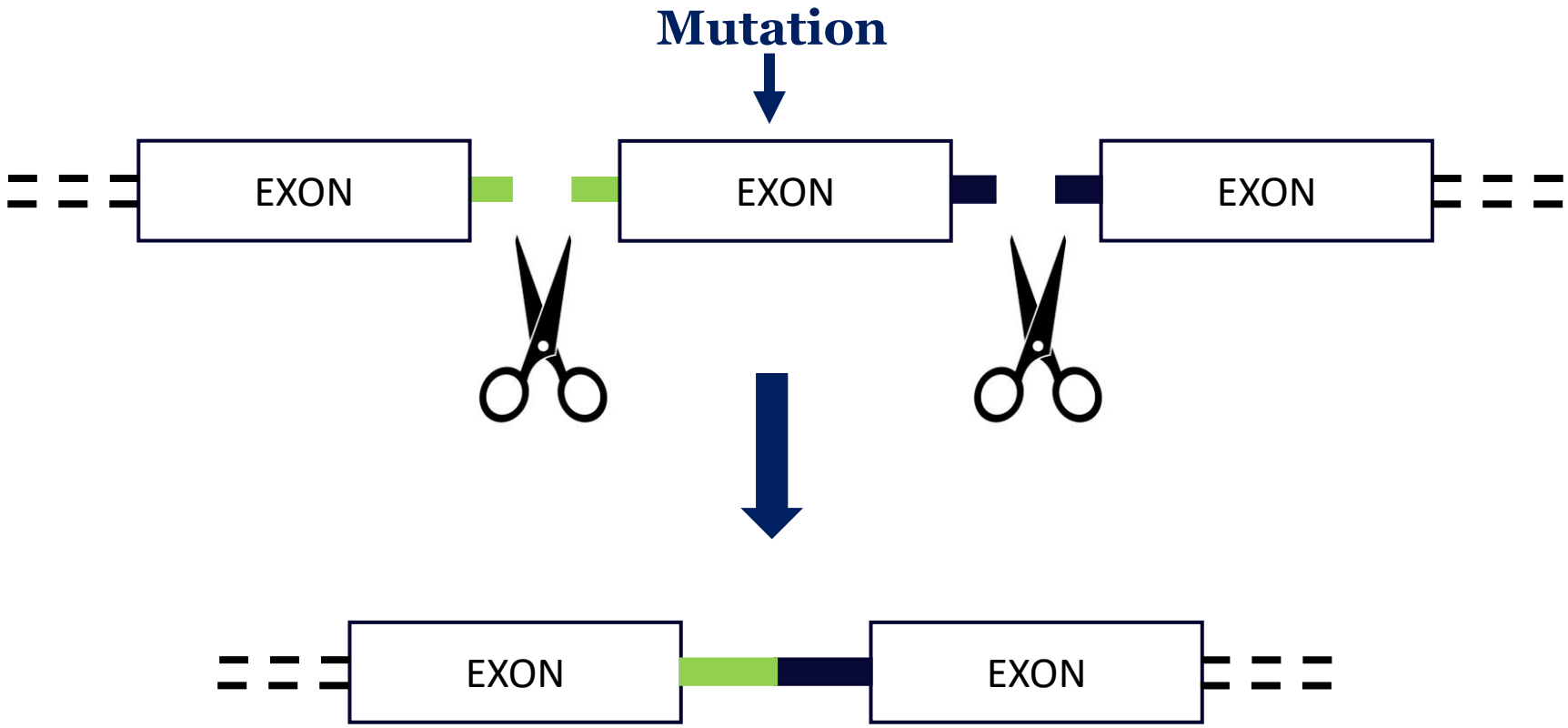
Casgevy for Sickle Cell

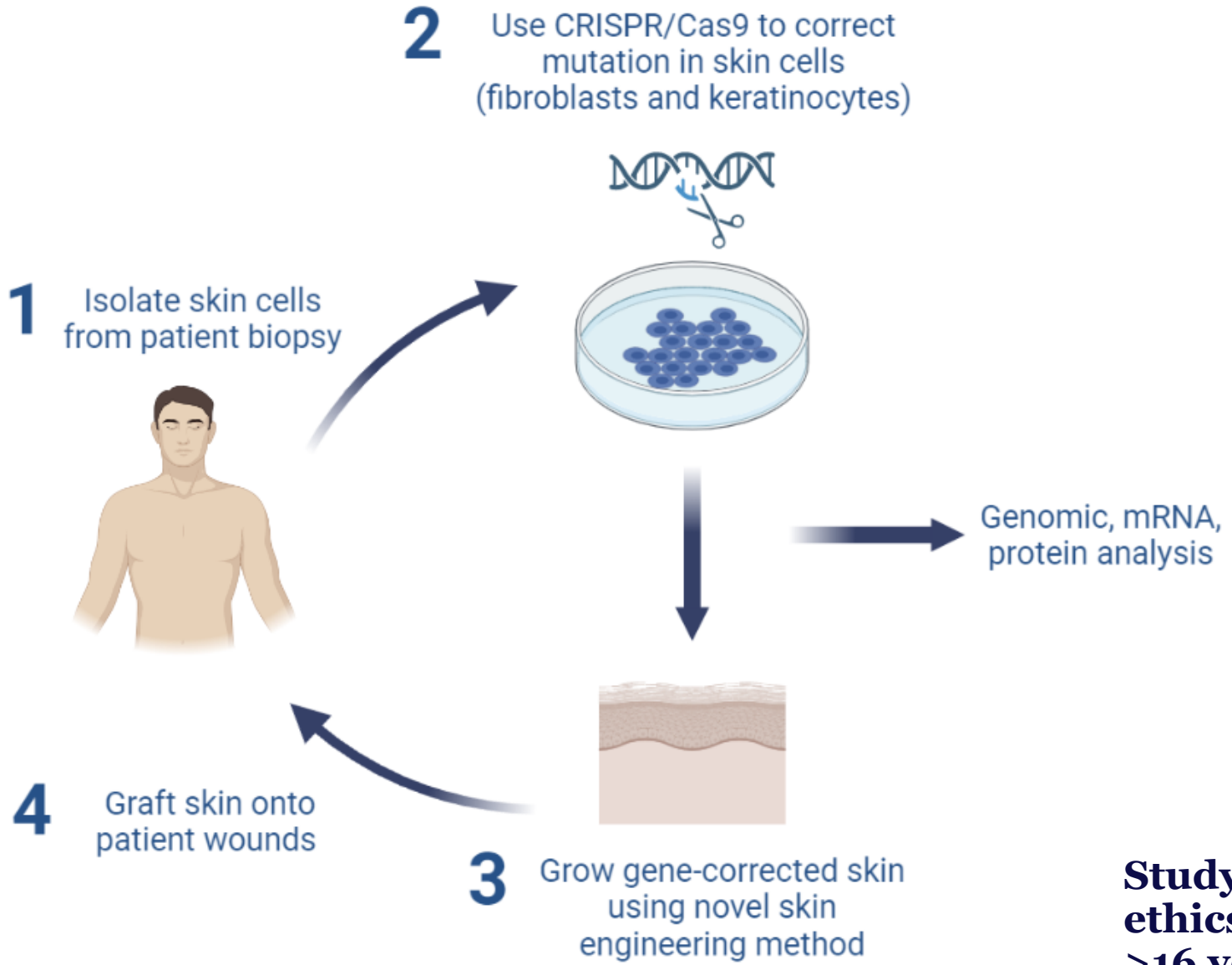




Cost- ~NZD4,400,000

CRISPR/Cas9 gene editing

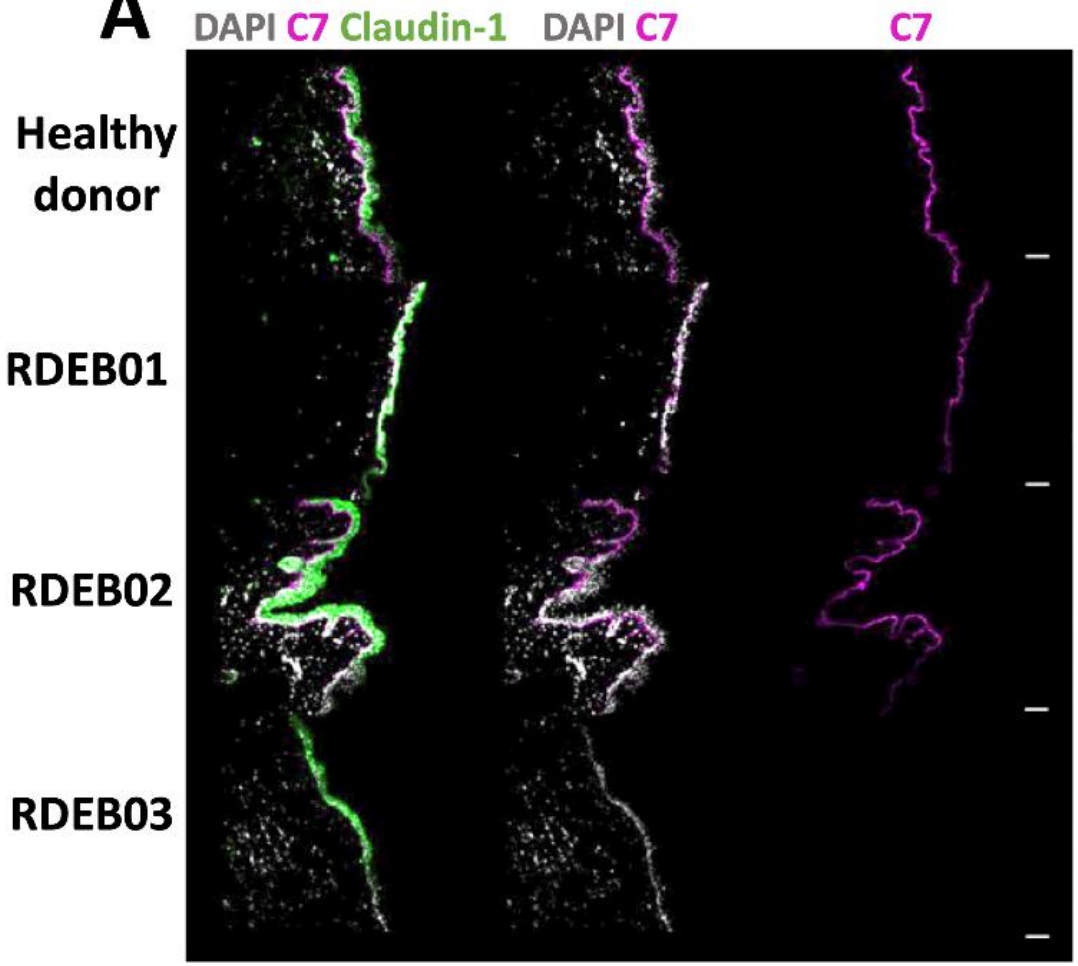




Study approved by national ethics committee in 2019 for >16 year olds only

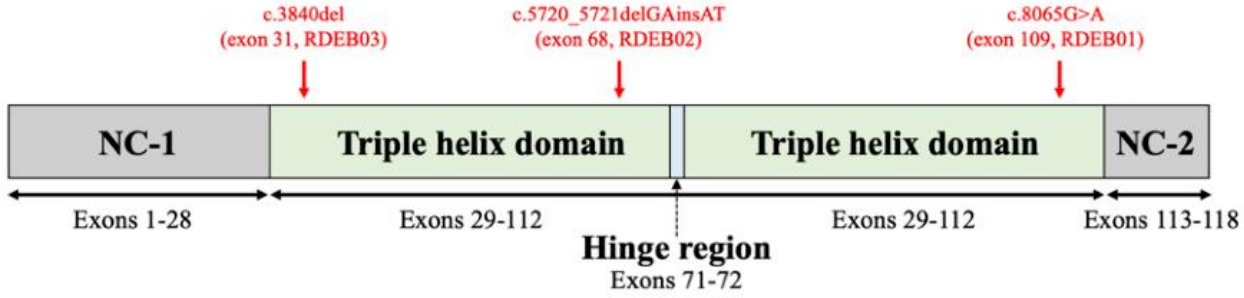
Five Enrolled Donors

A



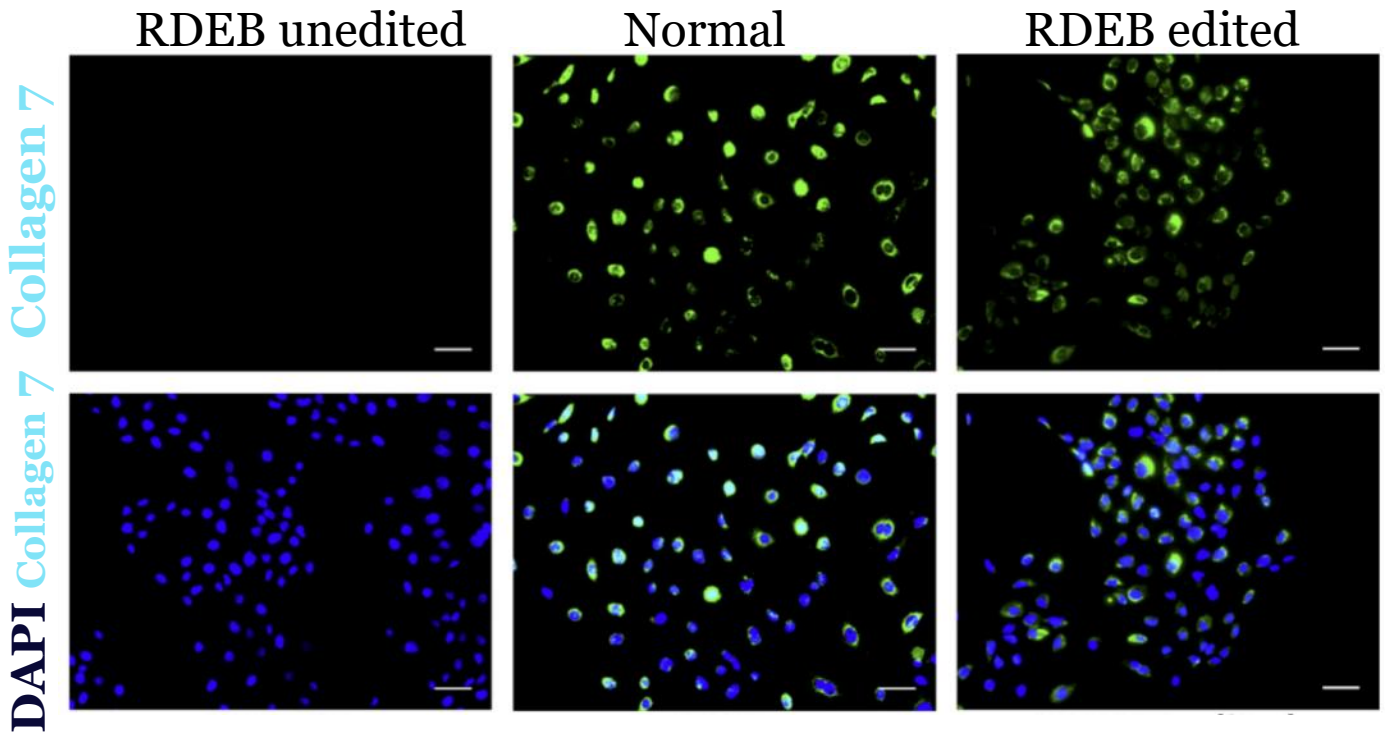
B

Donor	*COL7A1* mutations
RDEB01	Allele 1: c.2778_2779del Allele 2: **c.8065G>A**
RDEB02	Allele 1: c.550A>T Allele 2: **c.5720_5721delGAinsAT**
RDEB03	Allele 1: c.8698_8708del, Allele 2: **c.3840del**, c.8780G>A

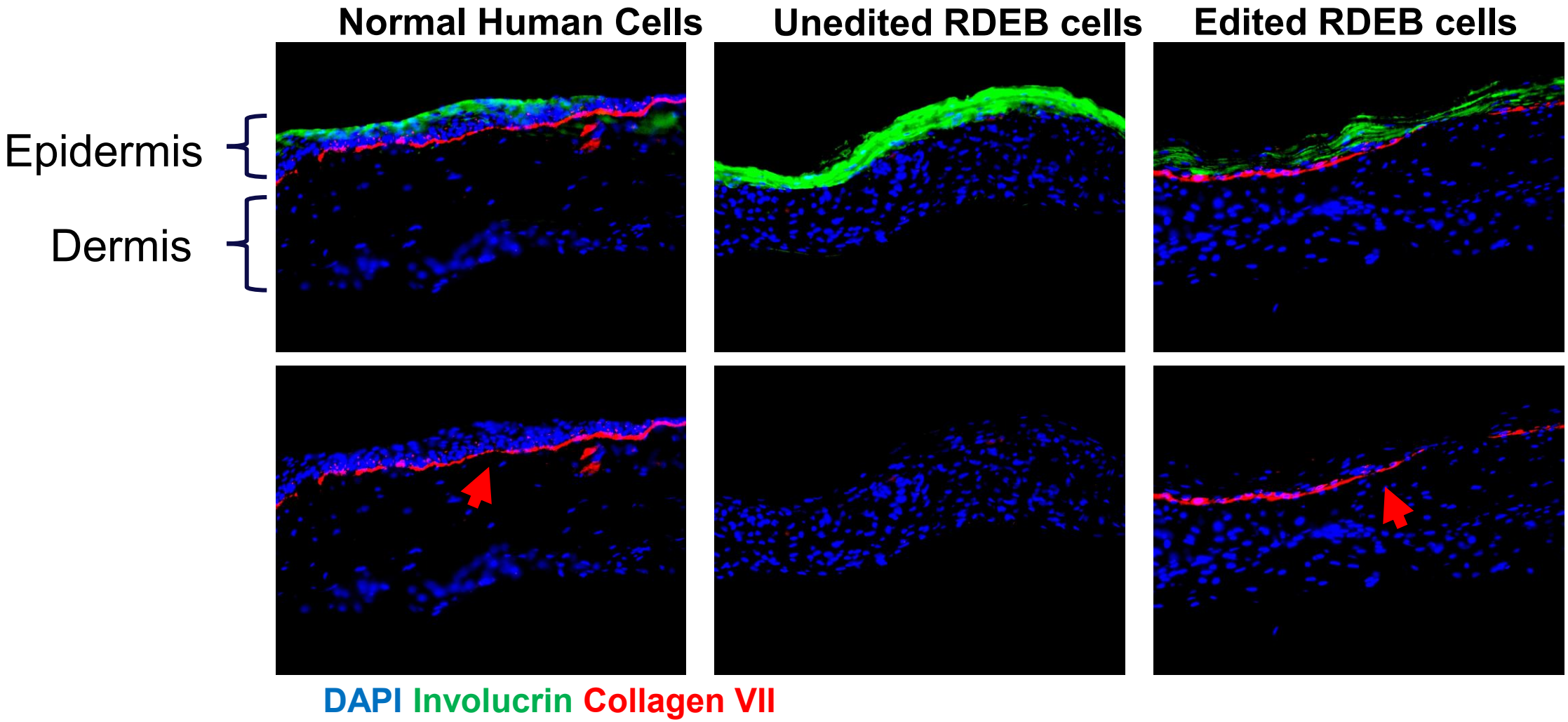


C

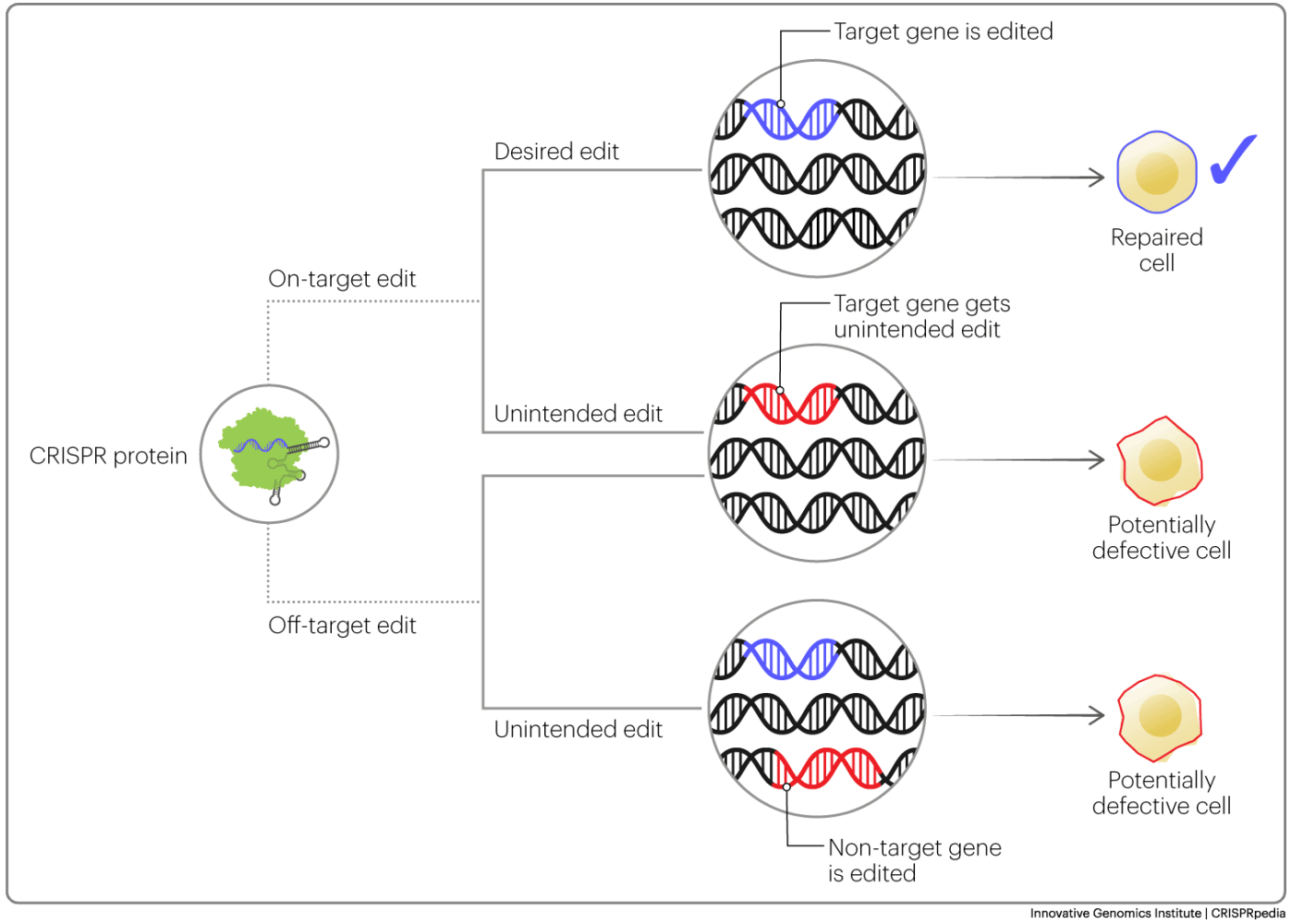
Gene editing restores Col7 expression



Gene editing restores Col7 expression

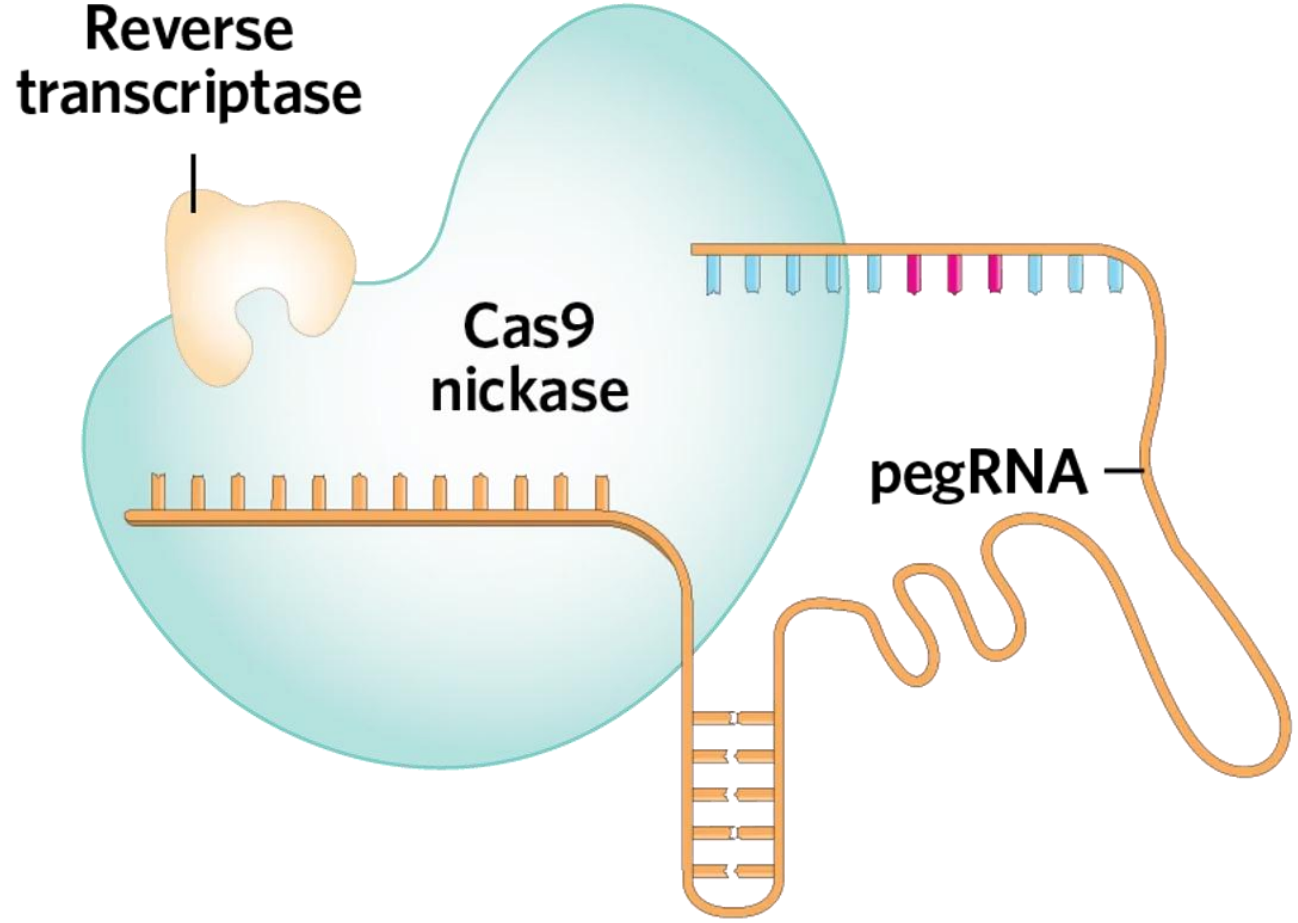


Unintended Effects



https://innovativegenomics.org/crisprpedia/crispr-ethics/

Prime Editing – the next generation of gene editing



Prime Editing –
Efficient and safer than Cas9 editing

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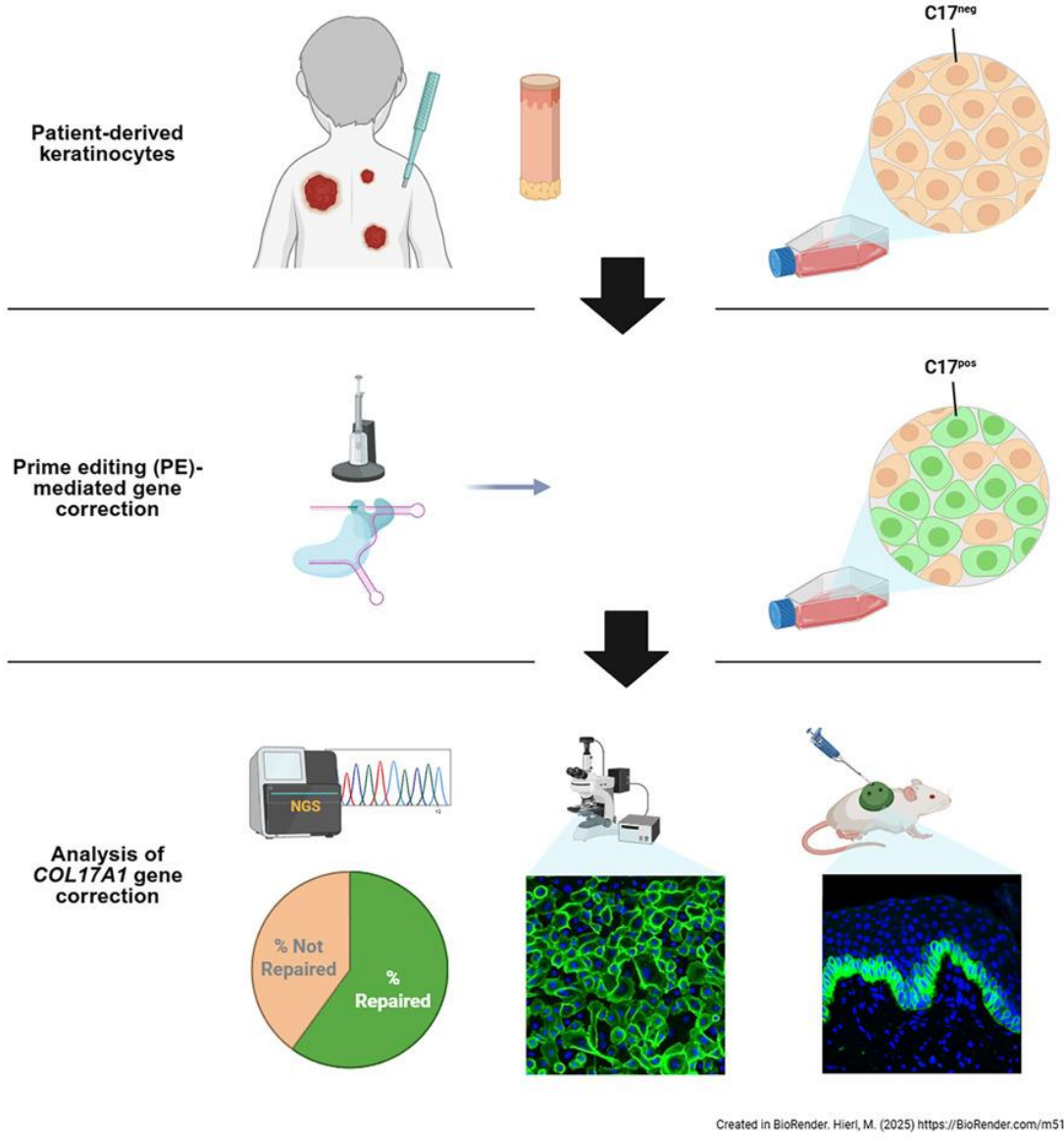
Prime editing as a promising therapeutic strategy for junctional epidermolysis bullosa

Markus Hierl [1,7] · Johannes Bischof [1] · Bernadette Liemberger [1] · Thomas Kocher [1] · Stefan Hainzl [1] · Stefanie Gruner [1] · Lisa Trattner [1] · Victoria Reichl [1] · Alfred Klausegger [1] · Clotilde Aussel [2,3] · Sandra Ammann [2,3] · Rebecca Raab [2,3] · Geoffroy Andrieux [4] · Martin Wolf [5,6] · Sarah Hochmann [5,6] · Patricia Ebner [5] · Verena Wally [1,10] · Roland Zauner [1] · Christina Guttmann-Gruber [1] · Iris K. Gratz [1,7,8] · Josefina Piñón Hofbauer [1] · Toni Cathomen [2,3,9] · Dirk Strunk [5,6] · Johann W. Bauer [10] · Ulrich Koller [1] ✉ Show less



Created in BioRender. Hierl, M. (2025) https://BioRender.com/m51bi

LNPs with lasers–
For topical delivery of gene editing

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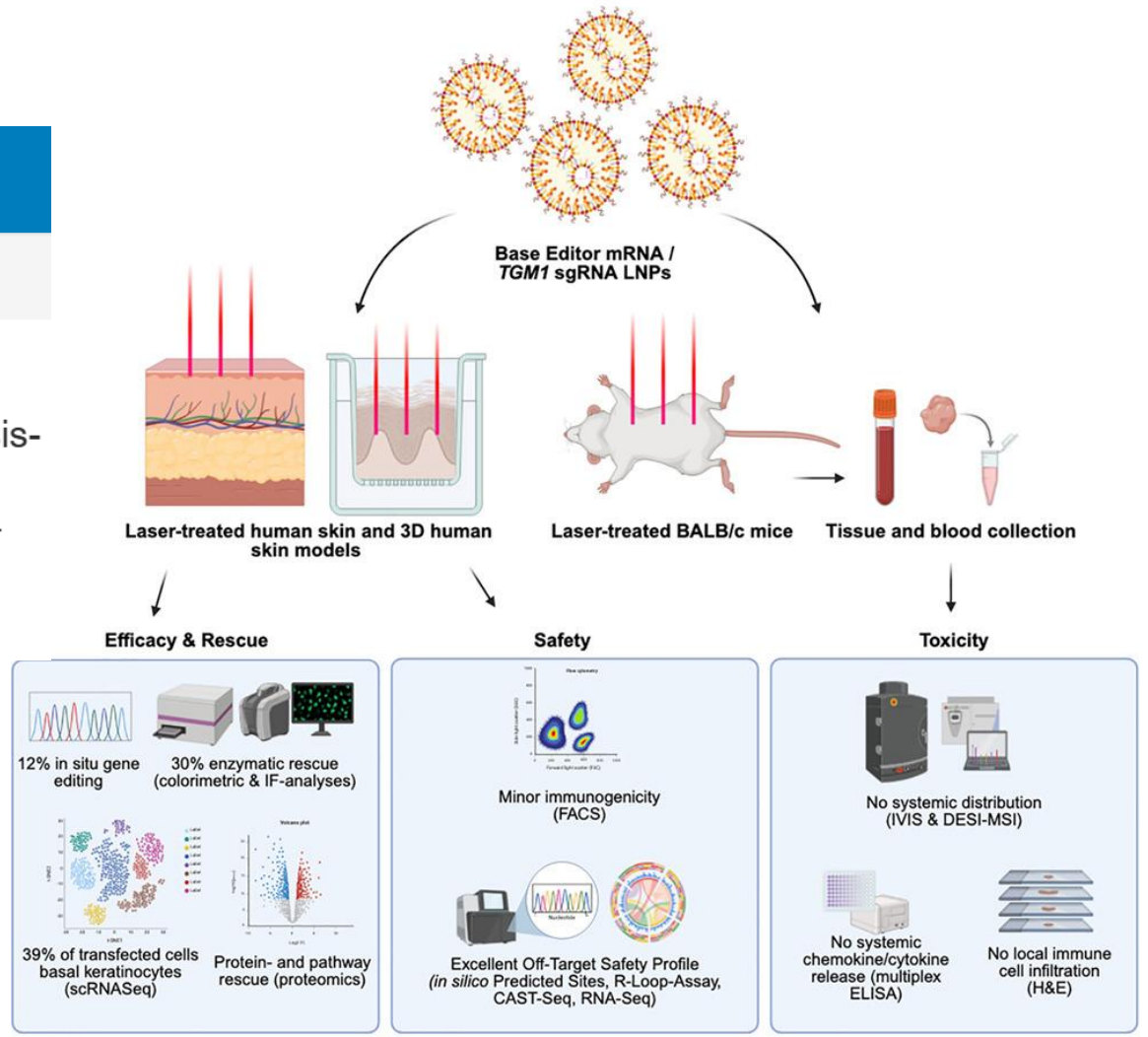
Lipid nanoparticle-based non-viral *in situ* gene editing of congenital ichthyosis-causing mutations in human skin models

Dilem Ceren Apaydin [1,12] · Gaurav Sadhnani [1,12] · Tiffany Carlaw [2] · Jan Renziehausen [1] · Elena Lizunova [1] · Viviane Filor [3] · Anna Hiller [1] · Sophia Brumhard [1] · Vincent Halim [4] · Ulrike Brüning [1] · Johannes Bischof [5] · Rafaela Horbach Marodin [6] · Daniel Z. Kurek [6] · Manuel Rhiel [7,8] · Sandra Ammann [7,8] · Tatjana I. Cornu [7,8,9] · Toni Cathomen [7,8,9] · Leif Erik Sander [1] · Benedikt Obermayer [1] · Fabian Coscia [10] · Jennifer Kirwan [1] · Ulrich Koller [5] · Achim D. Gruber [11] · Wolfgang Bäumer [3] ·



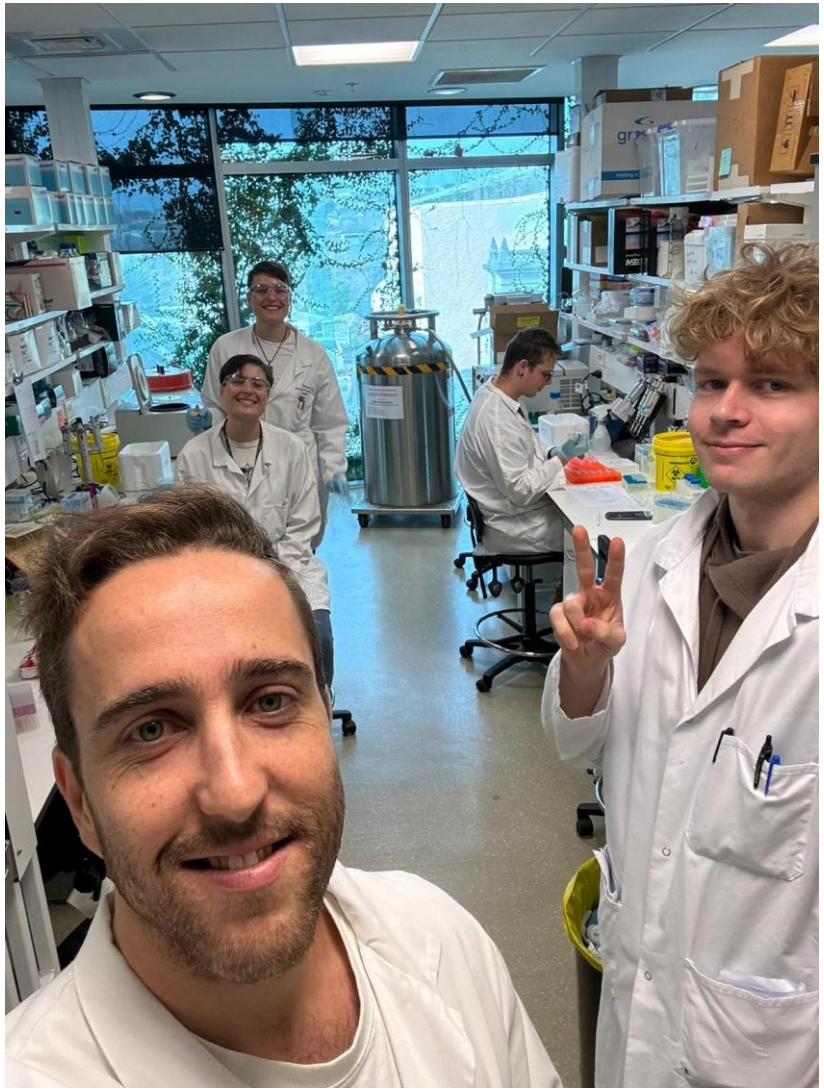
Conclusions

1. Gene editing therapies are already in the clinic – FDA approved

2. Gene editing is getting safer and more precise

3. The field is moving towards topical delivery

4. Progress is slow – and current therapies are very expensive



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Hunt JMT, du Rand A, Verdon D, Clemance L, Loef E, Malhi C, Buttle B, Knapp DJ, Michaels YS, Garlick J, Dunbar PR, Purvis D, Feisst V, Sheppard H. (2025) Enhanced HDR Mediated Correction of Heterozygous COL7A1 Mutations for Recessive Dystrophic Epidermolysis Bullosa, Molecular Therapy: Nucleic Acid, doi: https://doi.org/10.1016/j.omtn.2025.102472.

du Rand A, Hunt JMT, Verdon D, Buttle B, Dunbar PR, Purvis D, Feisst V, Sheppard H. (2024) Efficient dual Cas9 nickase correction of a prevalent pathogenic LAMB3 variant for junctional epidermolysis bullosa. JID Innovations, 100343,https://doi.org/10.1016/j.xjidi.2024.100343.

du Rand, A., Hunt, J.M.T., Samson, C.A., Dunbar, P.R., Purvis, D., Feisst, V., and Sheppard, H. (2024) Highly efficient CRISPR/Cas9-mediated exon skipping for recessive dystrophic epidermolysis bullosa. Bioeng and Trans Med DOI: 10.1002/btm2.10640

Acknowledgments

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Dan Verdon
Loef Evert

Auckland Genomics

Oxford University, UK

Tudor Fulga (Vertex)
Yale Michaels (Michigan)
David Knapp (Vancouver)

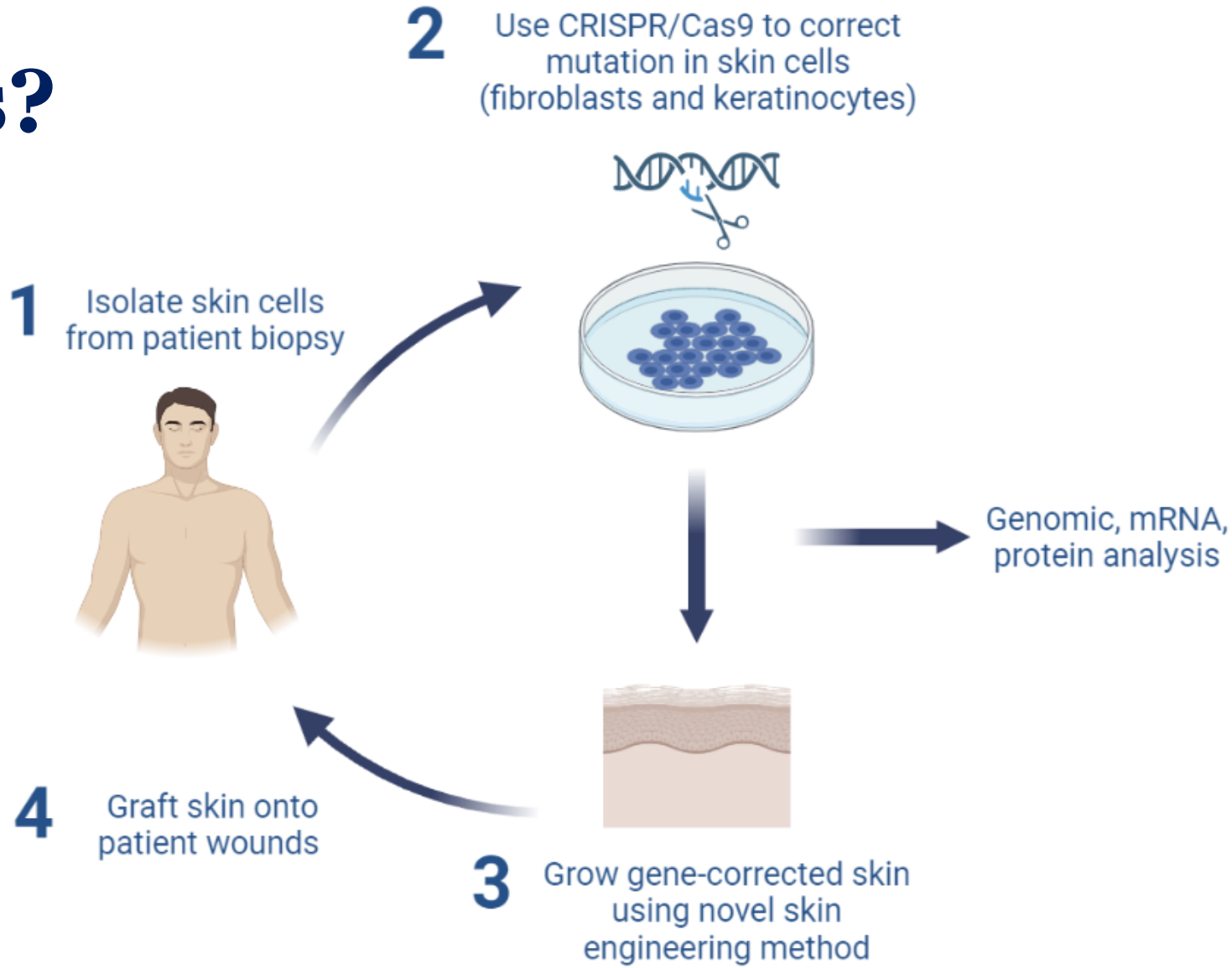
Clinicians

Diana Purvis (Starship)

Donors

People with EB
Healthy skin donors

Questions?


2
Use CRISPR/Cas9 to correct mutation in skin cells (fibroblasts and keratinocytes)
1
Isolate skin cells from patient biopsy
Genomic, mRNA, protein analysis
4
Graft skin onto patient wounds
3
Grow gene-corrected skin using novel skin engineering method