Inflammatory features in EB

John McGrath

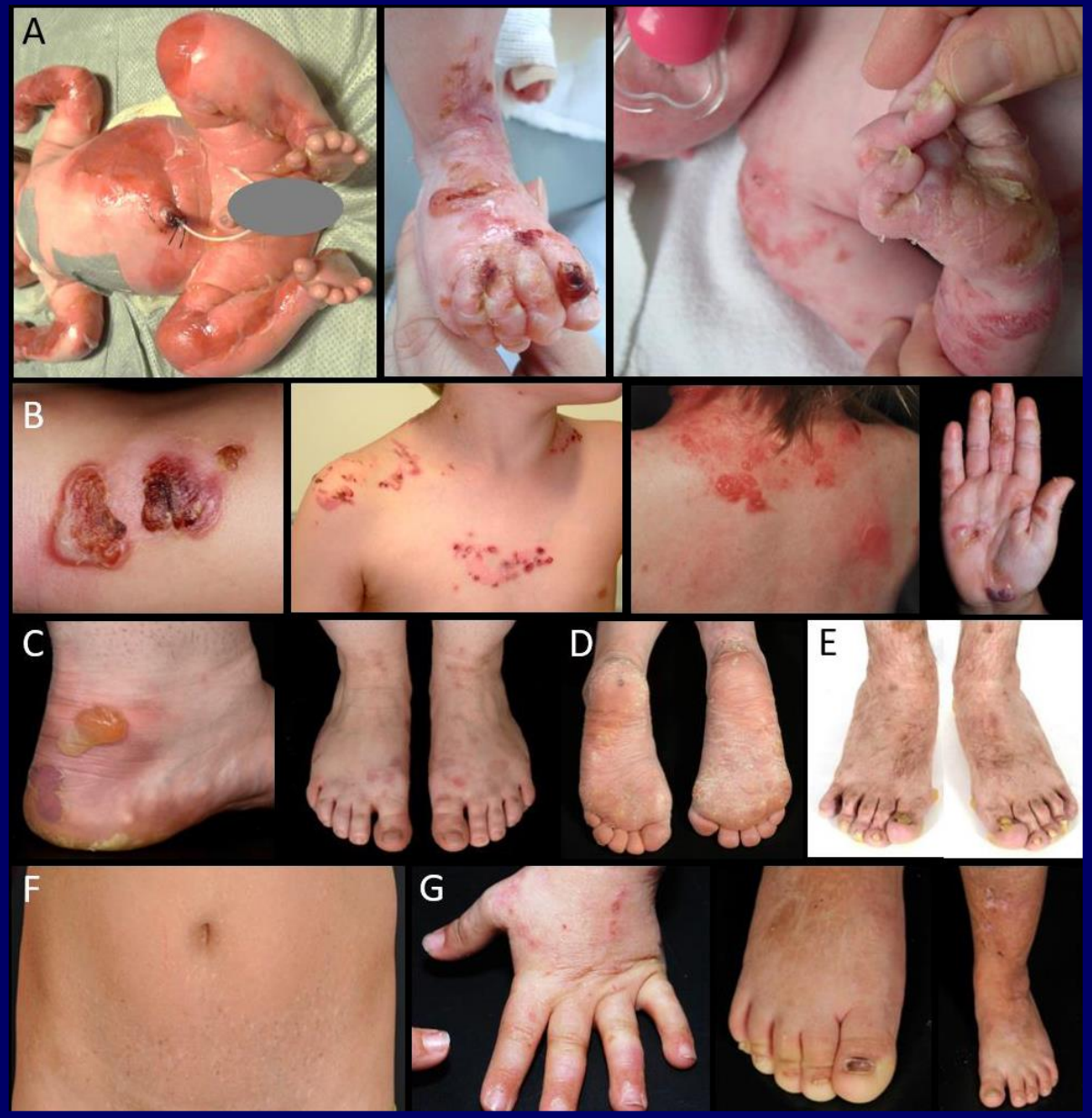
London UK

Has *et al.*
Br J Dermatol 2020

The challenges for people with various forms of EB are very different

Has *et al.*
Br J Dermatol 2020

EB SIMPLEX



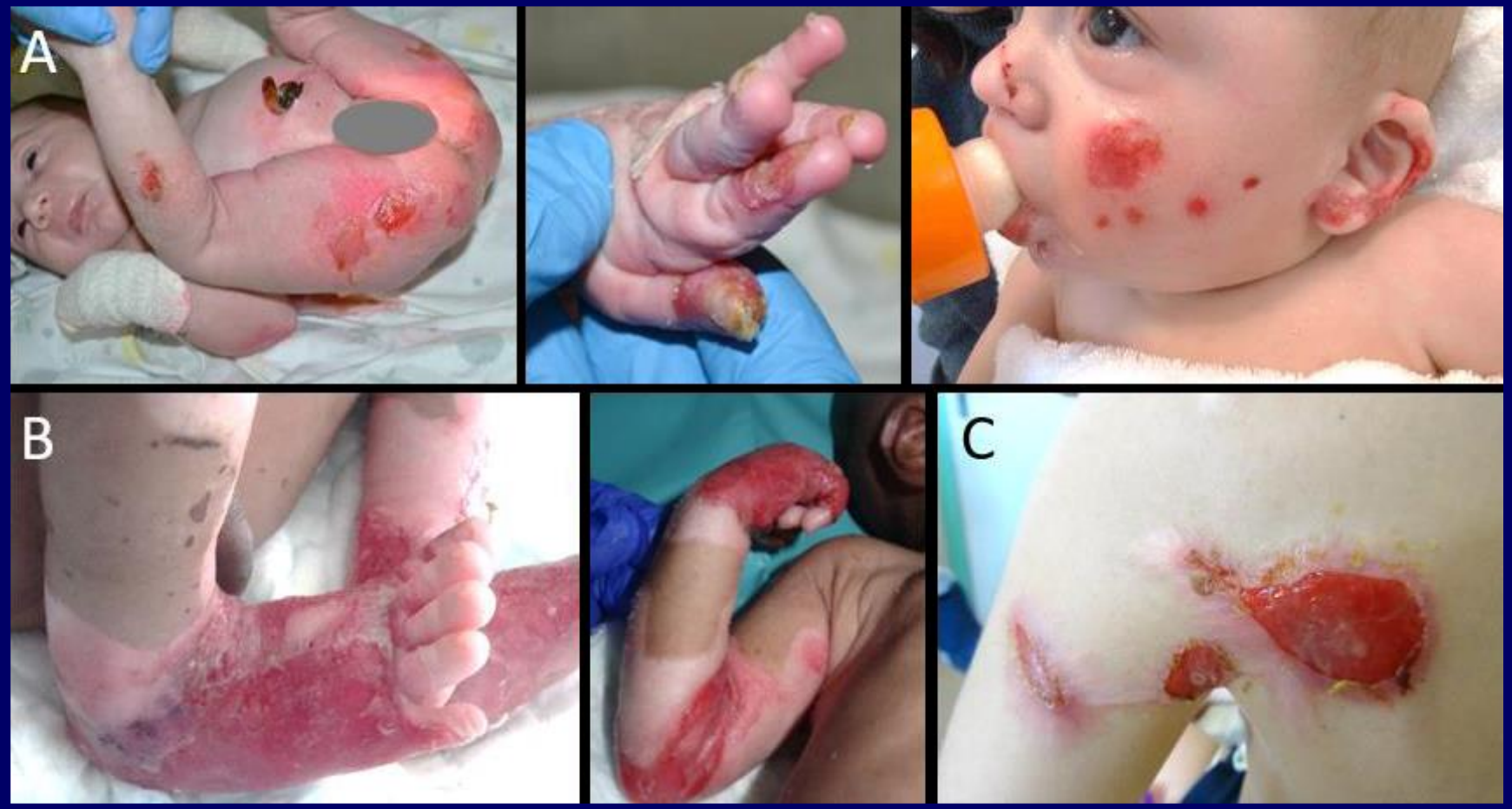
Most common form of EB

In some people blisters are localised and seasonal

Other individuals have more extensive blisters

Extracutaneous involvement can occur

JUNCTIONAL EB



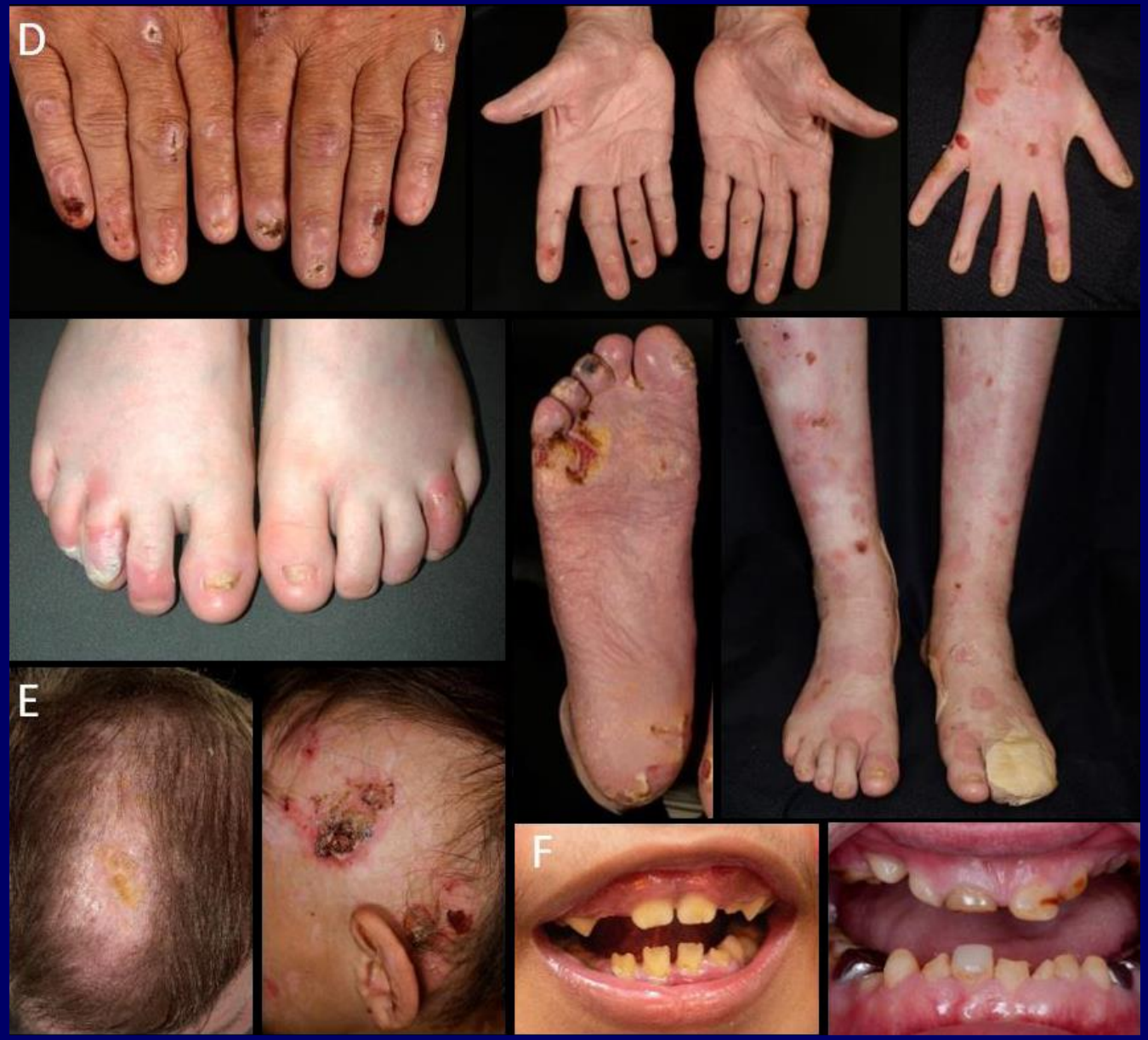
Rare form of EB

Some forms of JEB have a very poor prognosis

More localised with skin, hair, teeth, and nail manifestations

Extracutaneous involvement also may feature

JUNCTIONAL EB (milder)



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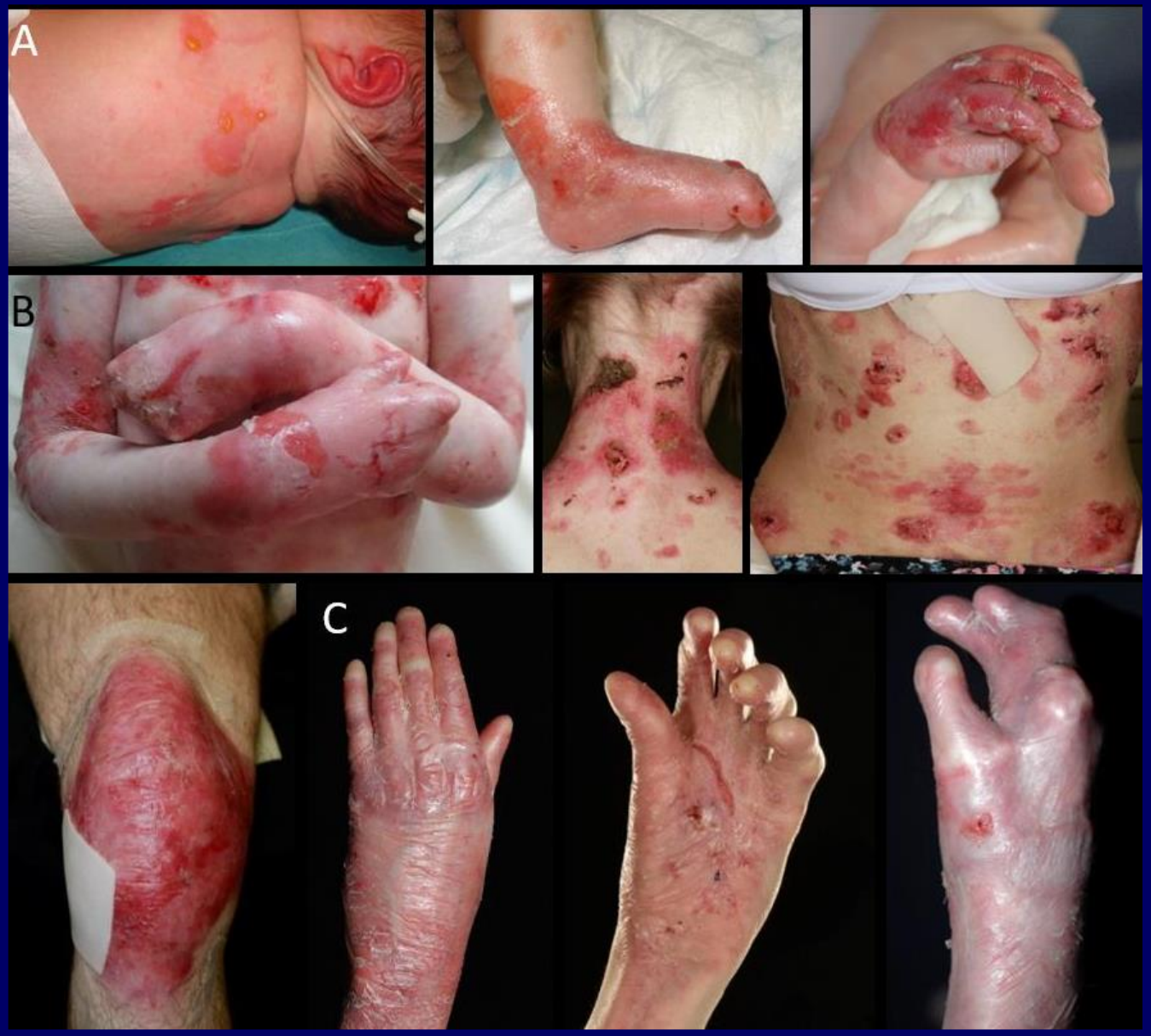
DYSTROPHIC EB



Autosomal dominant and recessive

Localised or generalised blistering

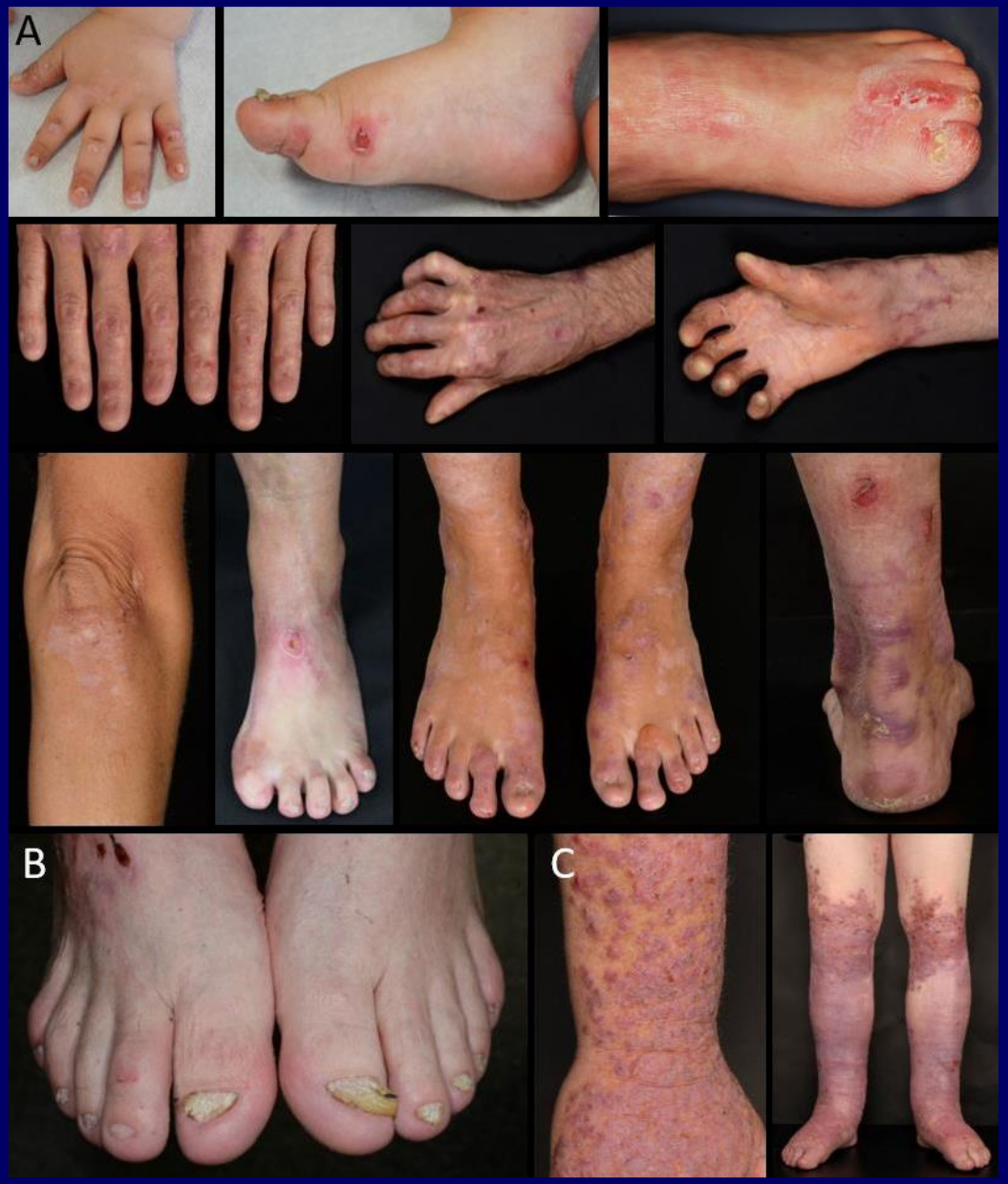
Itch, pain, scarring and contractures

Wounds may be slow to heal

Mucosal involvement

Increased risk of skin cancer (SCC)

DYSTROPHIC EB (milder)



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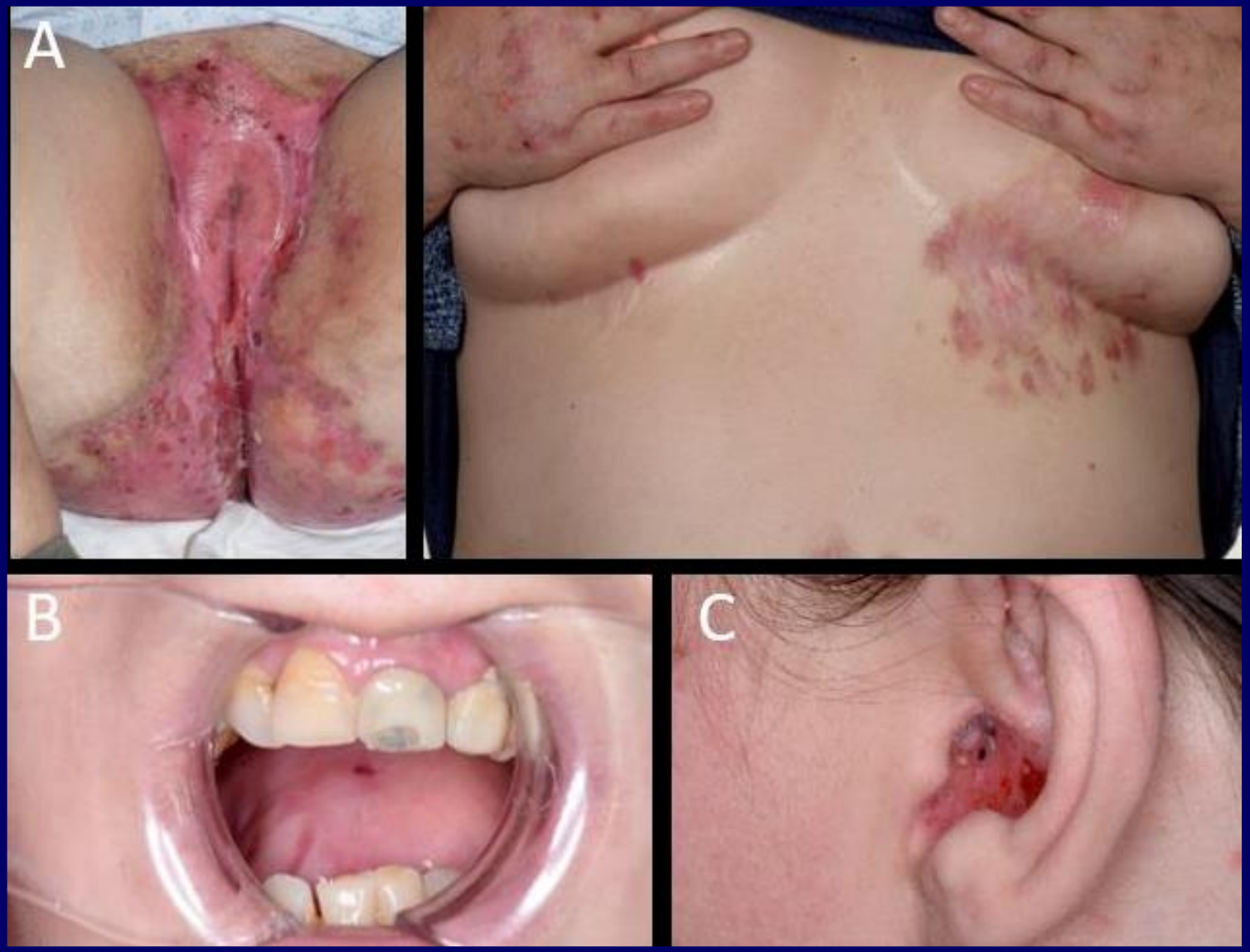

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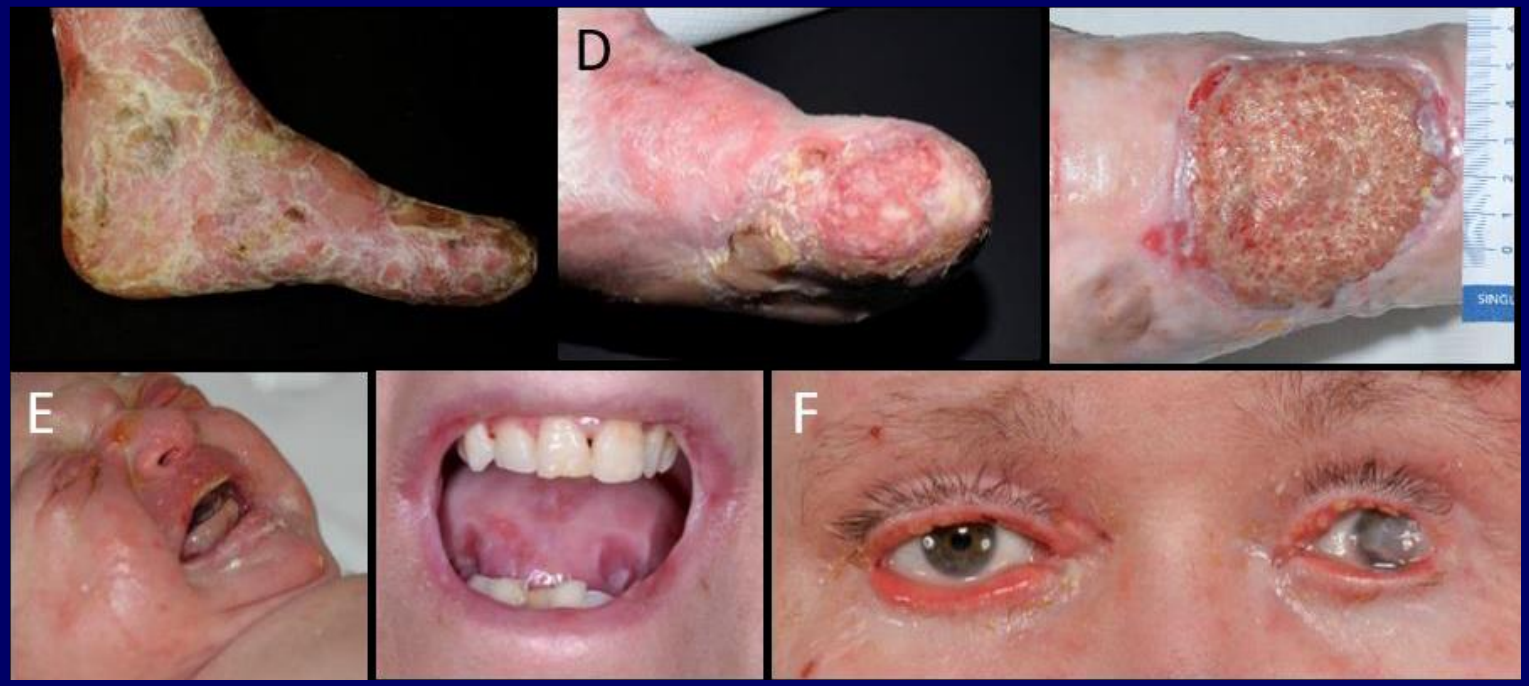

Autosomal dominant and recessive

Localised or generalised blistering

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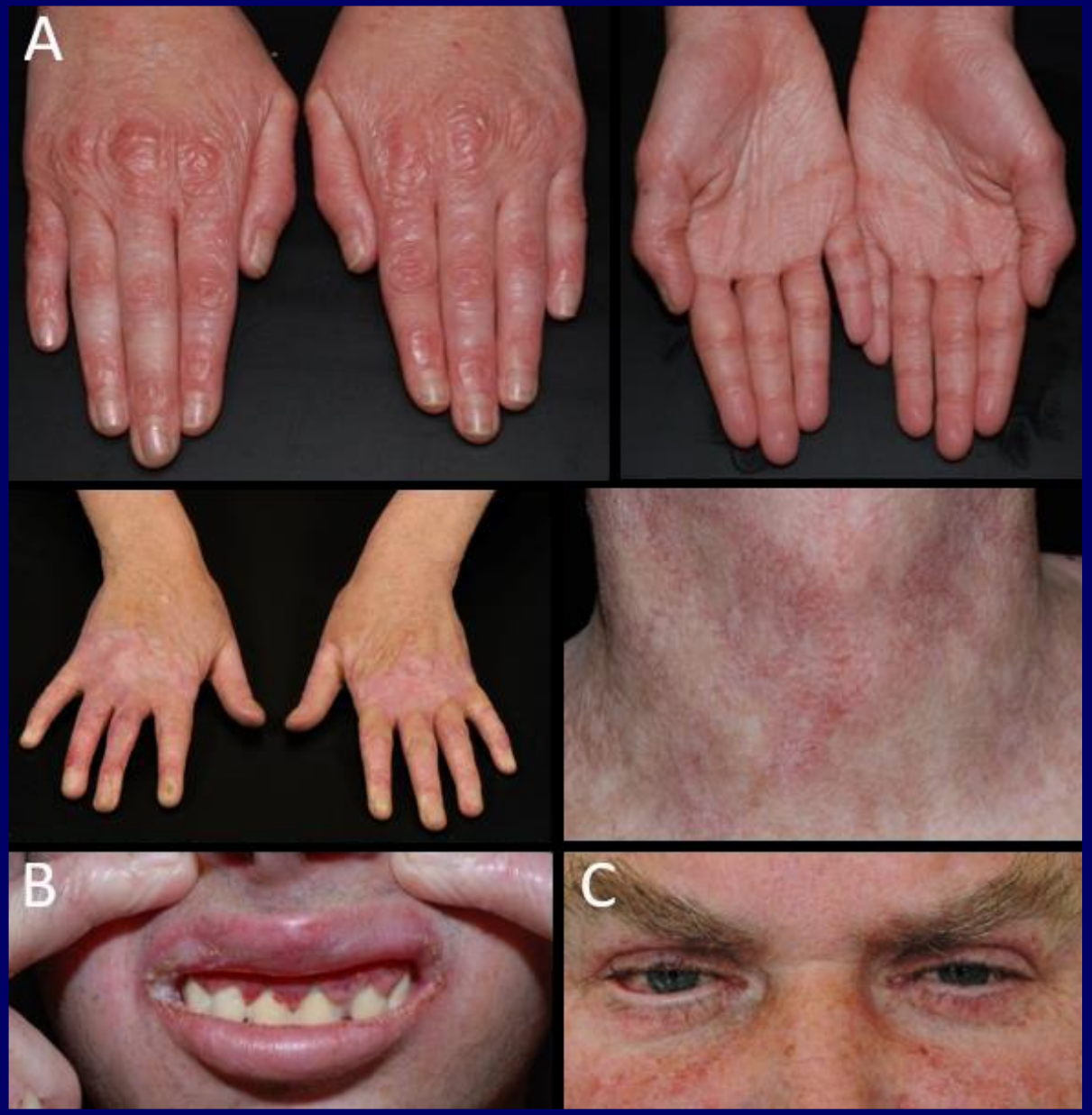
Wounds may be slow to heal

Mucosal involvement

Increased risk of skin cancer (SCC)

KINDLER EB



Initial blistering

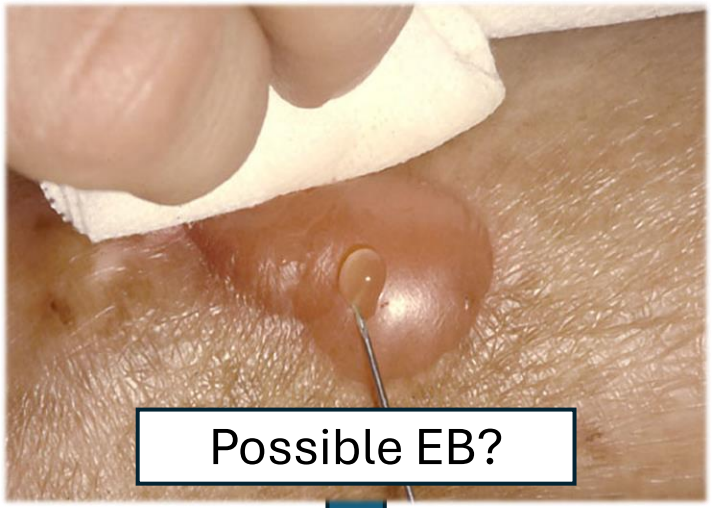
Then variable photosensitivity

Poikiloderma (especially atrophy)

Oral and mucosal involvement

Increased risk of skin cancer (SCC)

There have been huge advances in how we diagnose EB…



Possible EB?

Send blood or saliva to lab

Skin fragility NGS gene panel screening

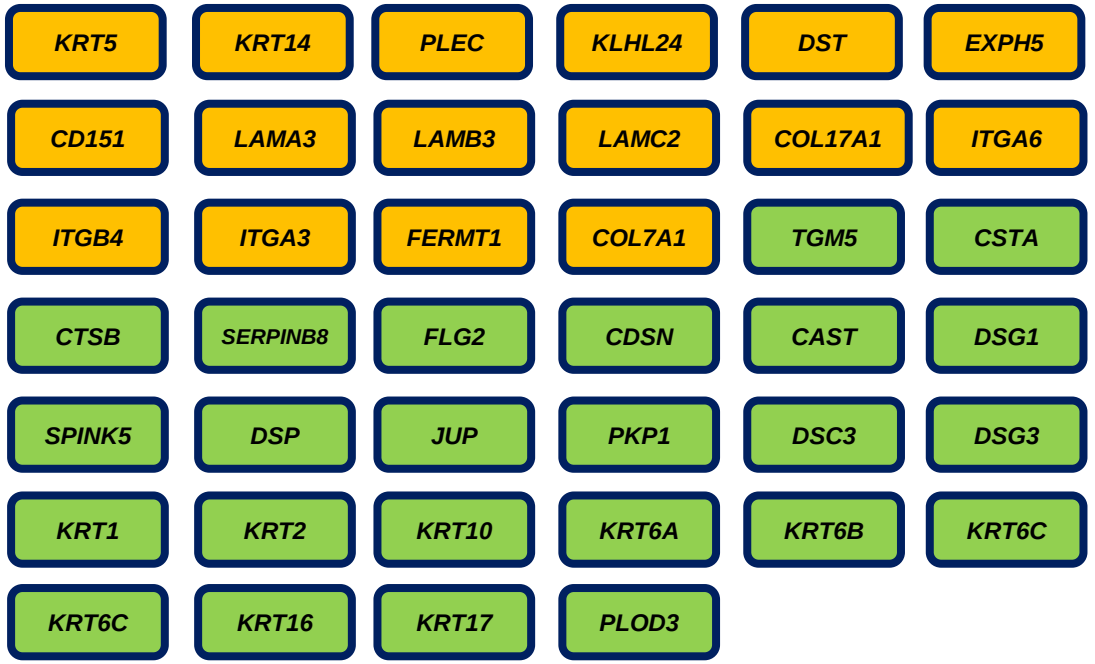
KRT5	KRT14	PLEC	KLHL24	DST	EXPH5
CD151	LAMA3	LAMB3	LAMC2	COL17A1	ITGA6
ITGB4	ITGA3	FERMT1	COL7A1	TGM5	CSTA
CTSB	SERPINB8	FLG2	CDSN	CAST	DSG1
SPINK5	DSP	JUP	PKP1	DSC3	DSG3
KRT1	KRT2	KRT10	KRT6A	KRT6B	KRT6C
KRT6C	KRT16	KRT17	PLOD3		

+/- p.(Arg125His) in *KRT14*

Autosomal Dominant Severe Epidermolysis Bullosa Simplex

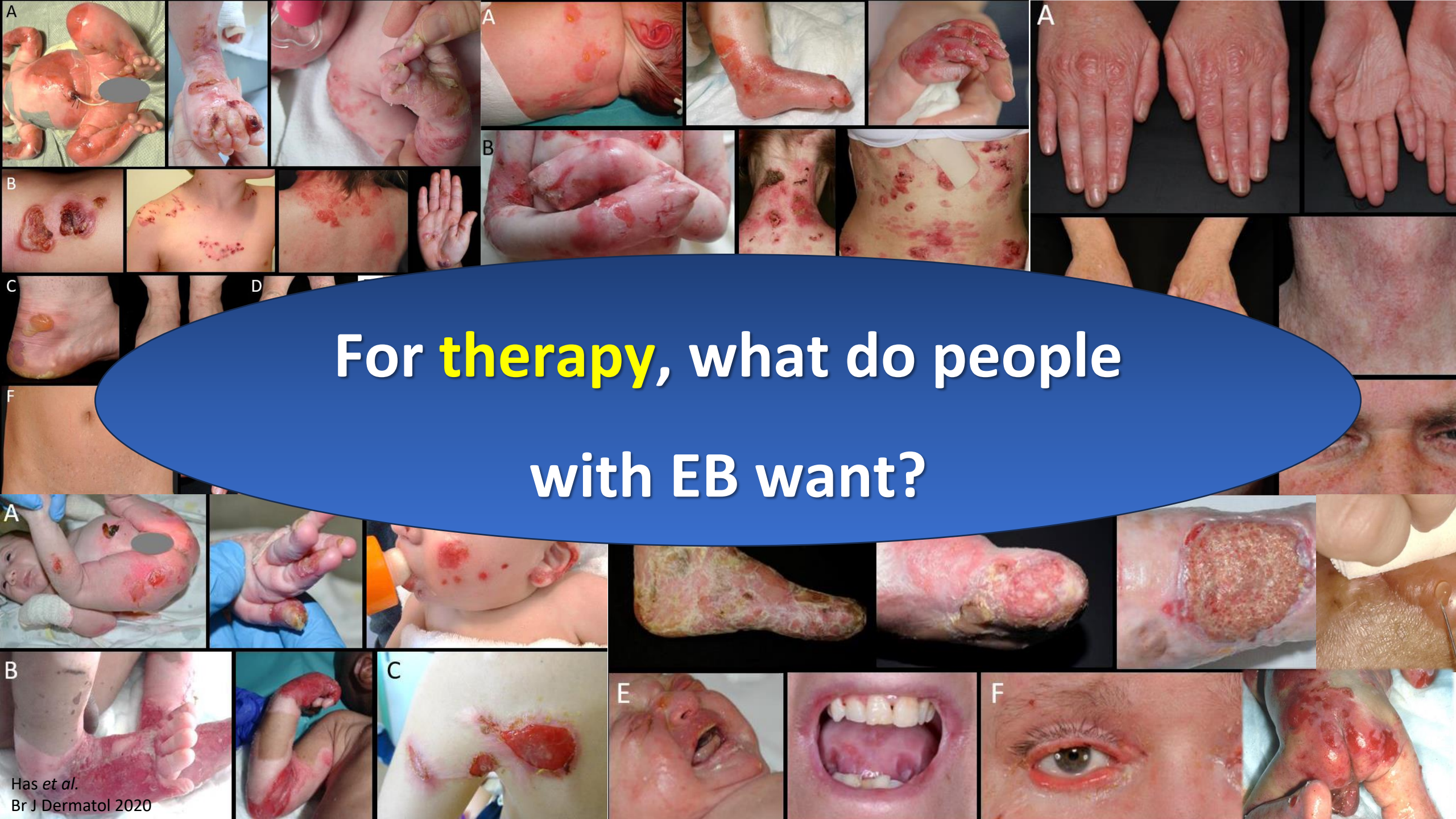
There have been huge advances in how we diagnose EB…

Forty genes to include in "gene therapy" based therapeutics



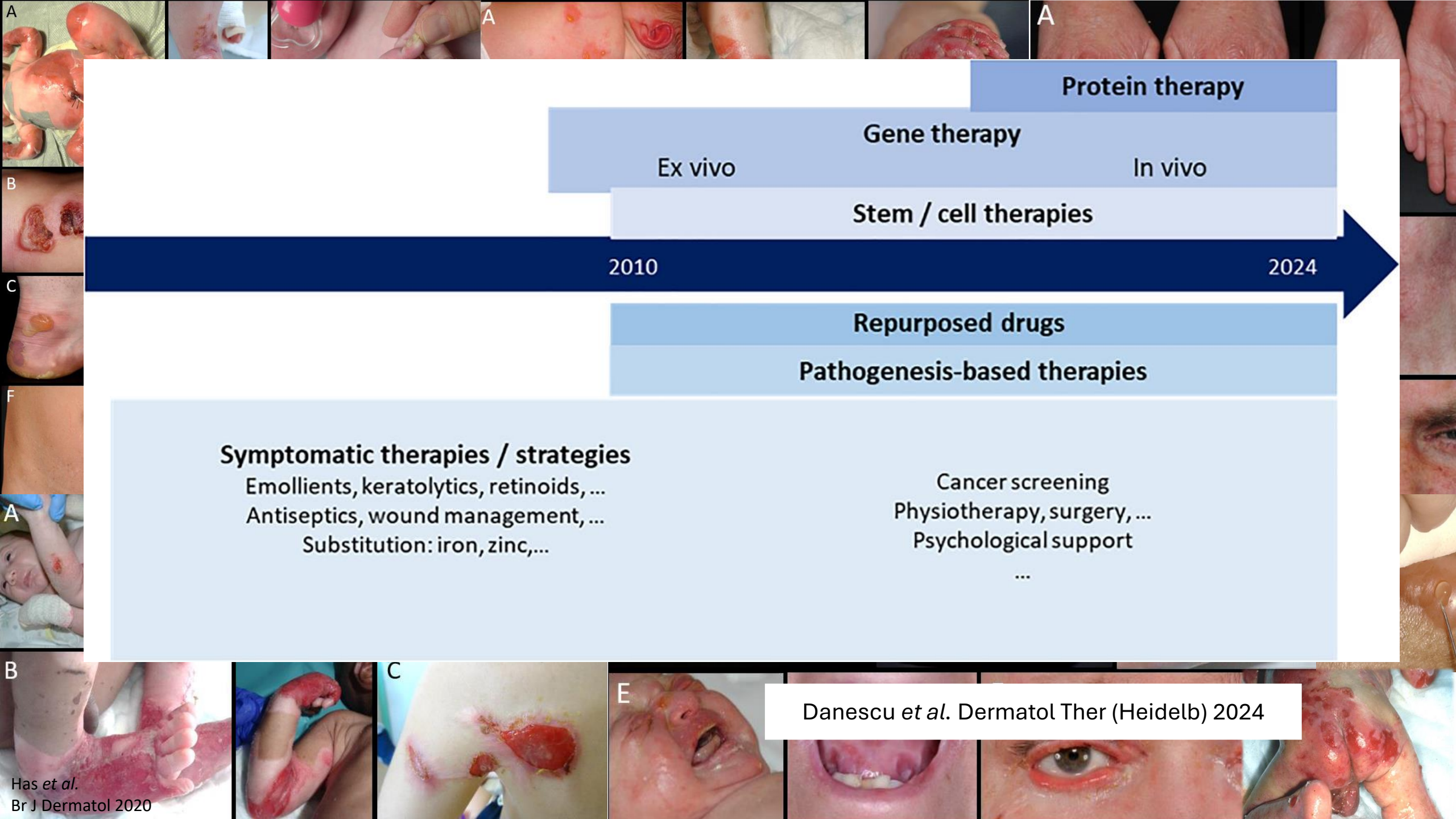
Most of the **pathogenic variants** in these 40 genes are **family-specific**

This presents a huge challenge for **gene corrective** therapies



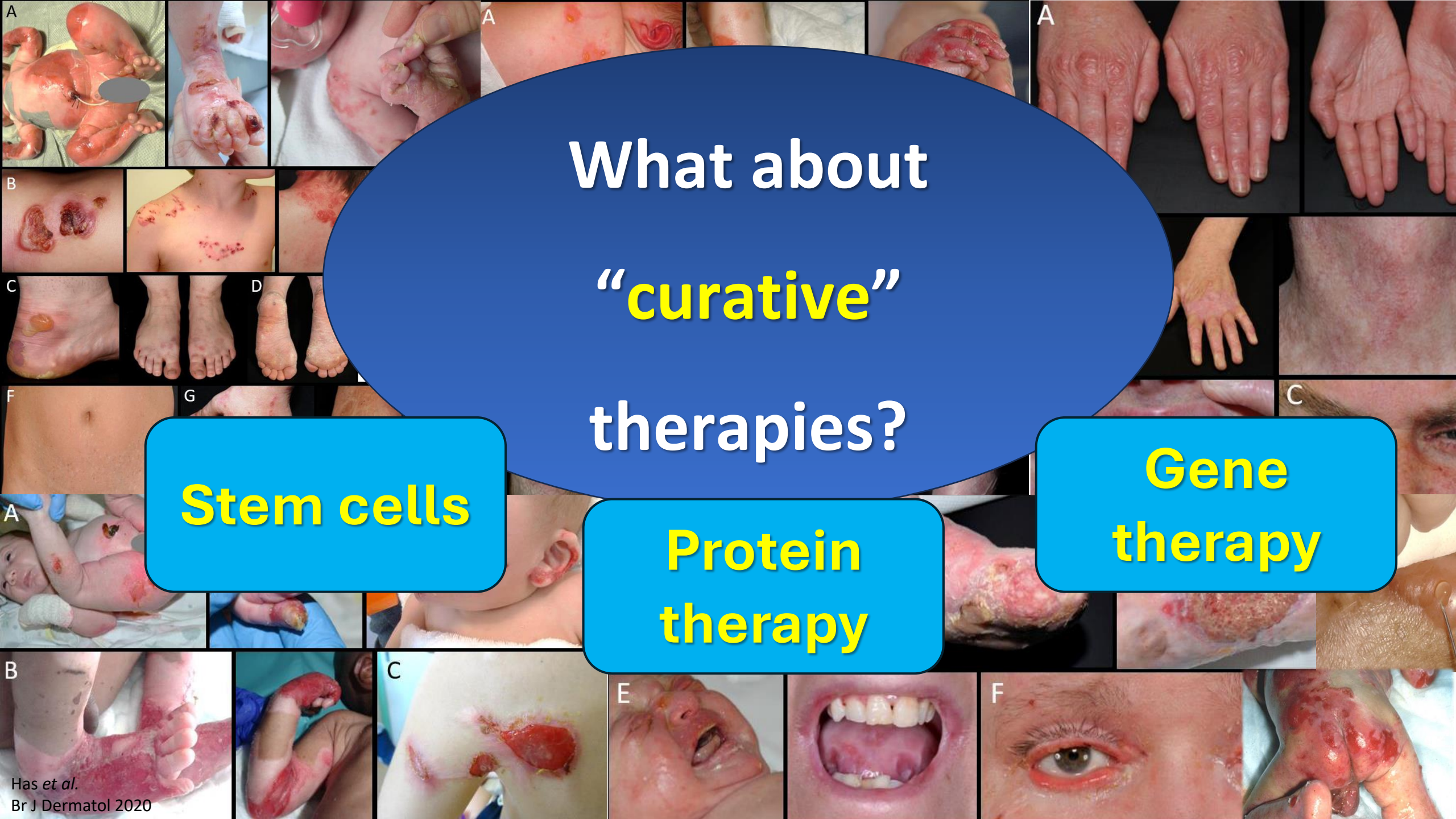
Has *et al.*
Br J Dermatol 2020


A cure!
Improved wound healing
Better symptom control
Better pain relief
Less itch
Has et al.
Br J Dermatol 2020

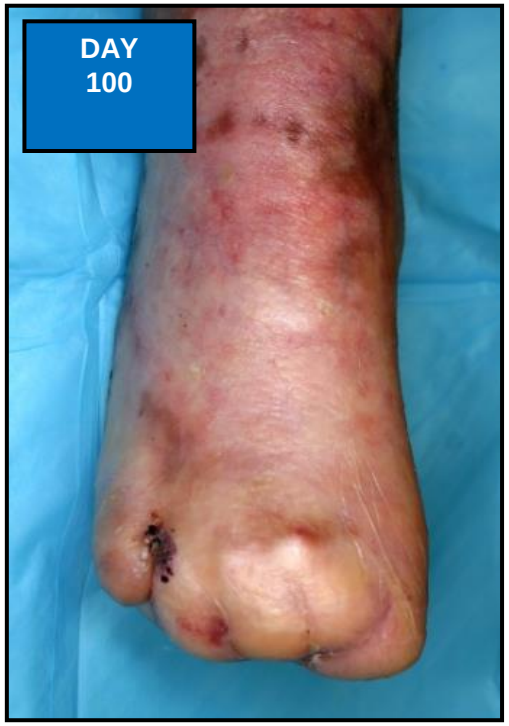


Danescu *et al.* Dermatol Ther (Heidelb) 2024

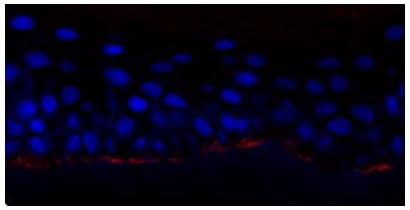
Has *et al.*
Br J Dermatol 2020

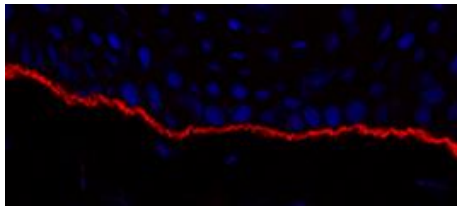

What about
"curative"
therapies?
Stem cells
Protein therapy
Gene therapy
Has *et al.*
Br J Dermatol 2020

Focus on Curing EB…

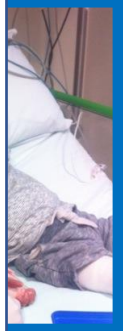


Wagner *et al.* NEJM 2010

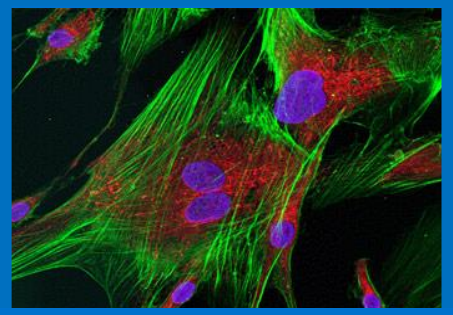




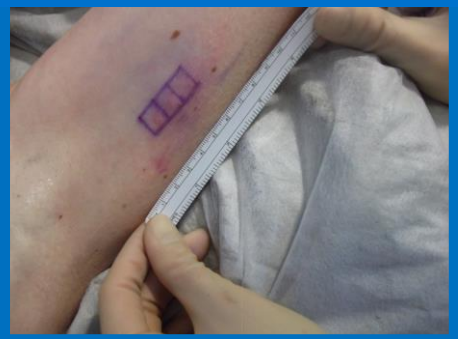
Bone Marrow Transplantation for RDEB



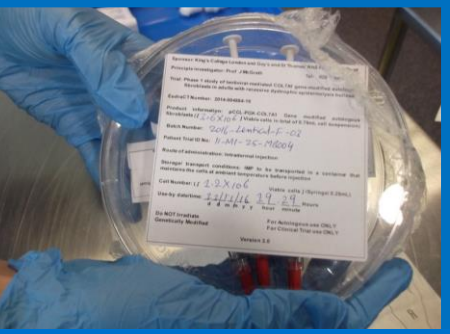
Stem Cell Therapy

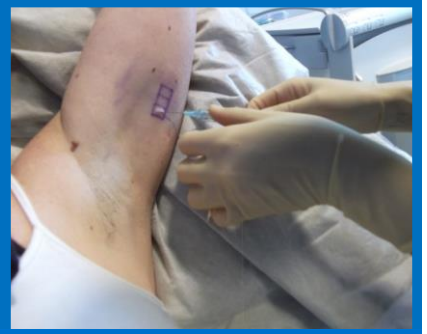


High mortality……. Mode of action?

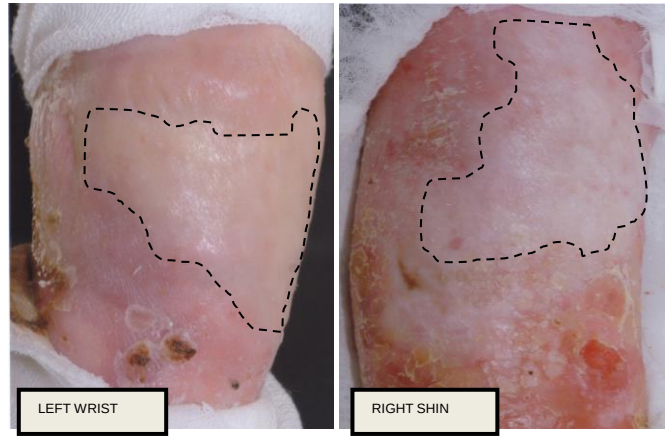



Corrective cell Therapy



Revertant mosaicism – natural gene therapy

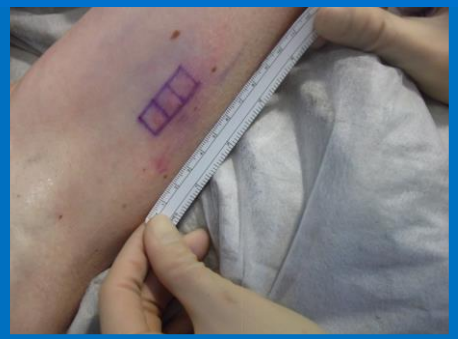


Grafting of cultured revertant keratinocytes

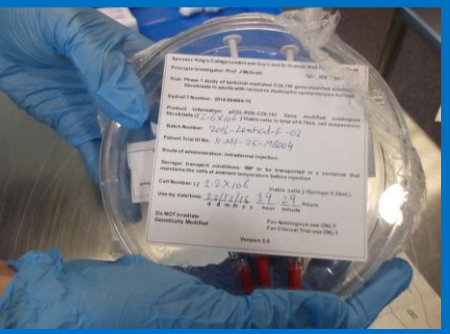
Gostynski *et al.* Br J Dermatol 2009

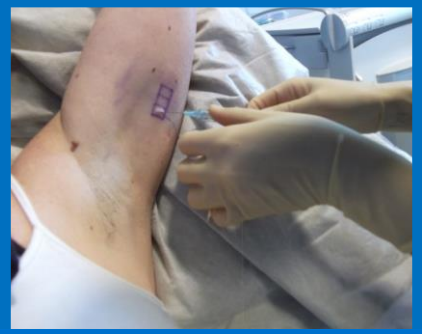
Punch grafting of revertant skin patches

Gostynski *et al.* J Am Acad Dermatol 2014

Corrective cell Therapy



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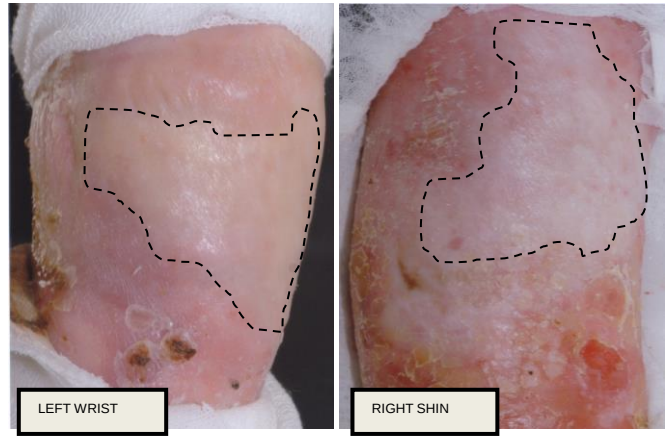
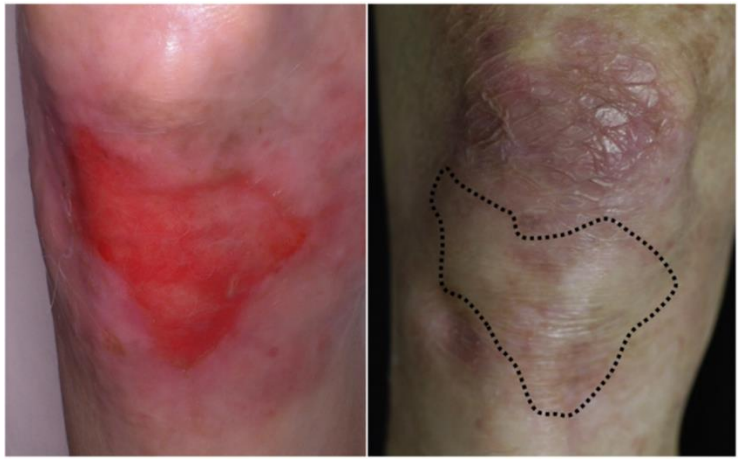


Cultured epithelial autografts from revertant mosaic skin



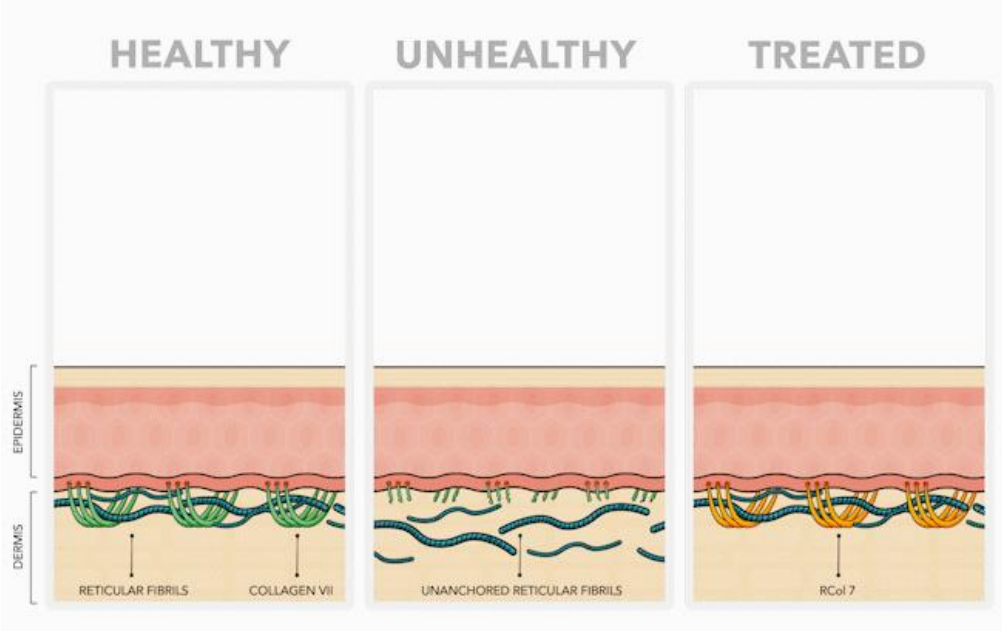
Matsumura *et al.*
J Invest Dermatol 2019

If the cause of RDEB is lack of type VII collagen – why can't you just give patients recombinant protein?

Phoenix Tissue Repair

Intravenous type VII collagen injections

- First trial started in February 2019



If the cause of RDEB is lack of type VII collagen – why can't you just give patients recombinant protein?

Interim update from a Phase 1/2 trial examining the safety and tolerability of PTR-01, a collagen 7 protein replacement therapy, in patients with recessive dystrophic epidermolysis bullosa

Anna L. Bruckner[1], Jean Tang[2], Mei Chen[3], David T. Woodley[3], Douglas Keene[4], Kathleen Peoples[1], Emily Gorell[2], Melissa Barriga[2], Hal Landy[5], Ramsey Johnson[5], Deborah Ramsdell[5]

[1]University of Colorado School of Medicine and Colorado Children's Hospital, Aurora, Colorado, USA
[2]Department of Dermatology, Stanford University School of Medicine, Redwood City, California, USA
[3]Department of Dermatology, The Keck School of Medicine, University of Southern California, Los Angeles, California, USA
[4]Shriner's Hospital for Children, Portland, Oregon, USA
[5]Phoenix Tissue Repair Inc., Boston, Massachusetts, USA

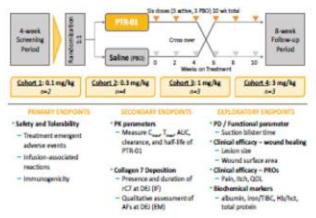
Background

- Dystrophic epidermolysis bullosa (DEB) is a rare genodermatosis due to mutations in the *COL7A1* gene encoding the α-chain of collagen 7 (C7). C7 deficiency results in dermal-epidermal junction (DEJ) separation with severe, painful blistering and scarring. Dominant (DDEB) and recessive (RDEB) forms occur. RDEB is typically more severe with wounds affecting not just skin but all mucosal membranes. Oral ulcers cause fusion of the tongue to the mouth floor and progressive microstomia. Esophageal erosions cause strictures and severe dysphagia requiring periodic dilatation. Nutritional deficiency and anemia are common. Corneal erosions can lead to scarring and loss of vision. Blistering and scarring of the hands and feet result in a characteristic pseudosyndactyly. The lifetime risk of aggressive squamous cell carcinoma is >90%.(1)
- The treatment of DEB is mainly palliative and none of the therapeutics currently in development address its systemic nature. PTR-01 is a recombinant human C7 given intravenously as replacement therapy. In mouse models of DEB, PTR-01 distributed to the DEJ, corrected dermal-epidermal separation and in mice, prolonged survival.(2) We describe interim results from a first-in-man study of PTR-01 in the treatment of adults with RDEB.

Methods

- Phase 1/2 randomized, double-blind, placebo-controlled, multiple dose, dose escalation, cross-over study in adults with genetically & histologically confirmed RDEB.
- Eligible patients are randomized to either PTR-01 or placebo in 4 dosing cohorts and receive 3 IV infusions at 2 week intervals. After a 2-week washout, the patient crosses over to the other treatment and receives 3 additional IV infusions. The patient is then observed for an additional 8 weeks.
- Dose and number of patients in each cohort are summarized in Figure 1, below.
- Primary endpoint of this first-in-man study of PTR-01 is safety, as measured by adverse events, infusion-associated reactions and immunogenicity.
- Secondary endpoints include pharmacokinetics (PK), deposition of PTR-01 at the dermal-epidermal junction (DEJ) by immunofluorescence and formation of anchoring fibrils by electron microscopy.
- Exploratory endpoints include suction blister time, wound healing, assessments of itch, pain and quality of life and nutritional markers.

Figure 1: Design of Study PTR-01-001



Results

Primary Outcome: Safety

- All 9 patients in Cohorts 1 – 3 completed dosing
- 36 treatment emergent AEs
  - No unexpected AEs
  - No serious AEs related to study drug based upon data as of 9 June 2020
  - 20 Not related, 6 Unlikely, 7 Possibly, 3 Probably
  - 22 Mild in severity, 6 Moderate (none related), 8 Severe (not related or unlikely related)
- 3 patients (2 in Cohort 2 and one in Cohort 3) developed low-titers of anti-drug antibodies which have declined over time
- 2 patients in Cohort 3 had mild infusion-associated reactions (IARs) characterized by flushing and mild increase in temperature
  - Events were brief and resolved spontaneously
  - Neither required dose adjustment, slowing of infusion or any other intervention
  - One had low levels of anti-drug antibodies which declined; the other has been negative

Secondary Outcomes: Pharmacokinetics (PK) and C7 in Tissue

Figure 2: PTR-01 Pharmacokinetics by Cohort

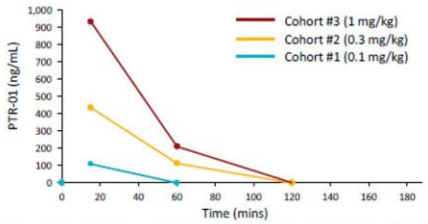


Figure 2. Serum PK shows linear dose response. Of note, only Cohort 3 (1 mg/kg) approaches the levels seen at the minimum effective dose in animal pharmacology studies.

Figure 3: C7 in Tissue by Direct Immunofluorescence: Cohort 3

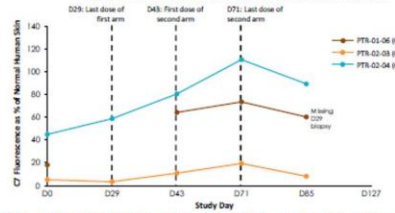


Figure 3. All 3 patients in Cohort 3 showed a 2 – 3 fold increase in C7 immunofluorescence following infusions of PTR-01.

Figure 4: C7 immunofluorescence in Cohort 3 patients

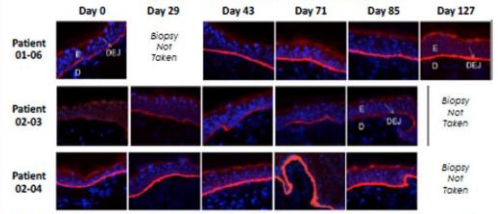


Figure 4. Immunofluorescence staining for C7 in patients in Cohort 3 showed increased C7 at the DEJ in unwounded skin after 3 infusions of PTR-01. Electron microscopy for anchoring fibrils did not show a change from Baseline at these timepoints. White arrow points to enhanced DEJ staining of C7 (average of 200% increase from baseline). We had limited AF data due to few intact biopsies.

Summary and Conclusions

In this short-term, first-in-man study, intravenous PTR-01 was safe and well-tolerated at doses up to 1 mg/kg. At the highest dose studied to date (1 mg/kg), an average increase in tissue C7 by immunofluorescence was noted. Modest positive trends were noted in pharmacodynamic markers, tissue C7 content. Modest positive trends were noted in a pharmacodynamic marker, patient reported outcomes and wound healing. PK data, interpreted in the context of previous animal data, suggest the need for a higher dose of PTR-01 which is being investigated in Cohort 4. Longer term studies will be needed to confirm PTR-01's anticipated effects on systemic features of DEB such as esophageal strictures, pseudosyndactyly, corneal abrasions, etc.

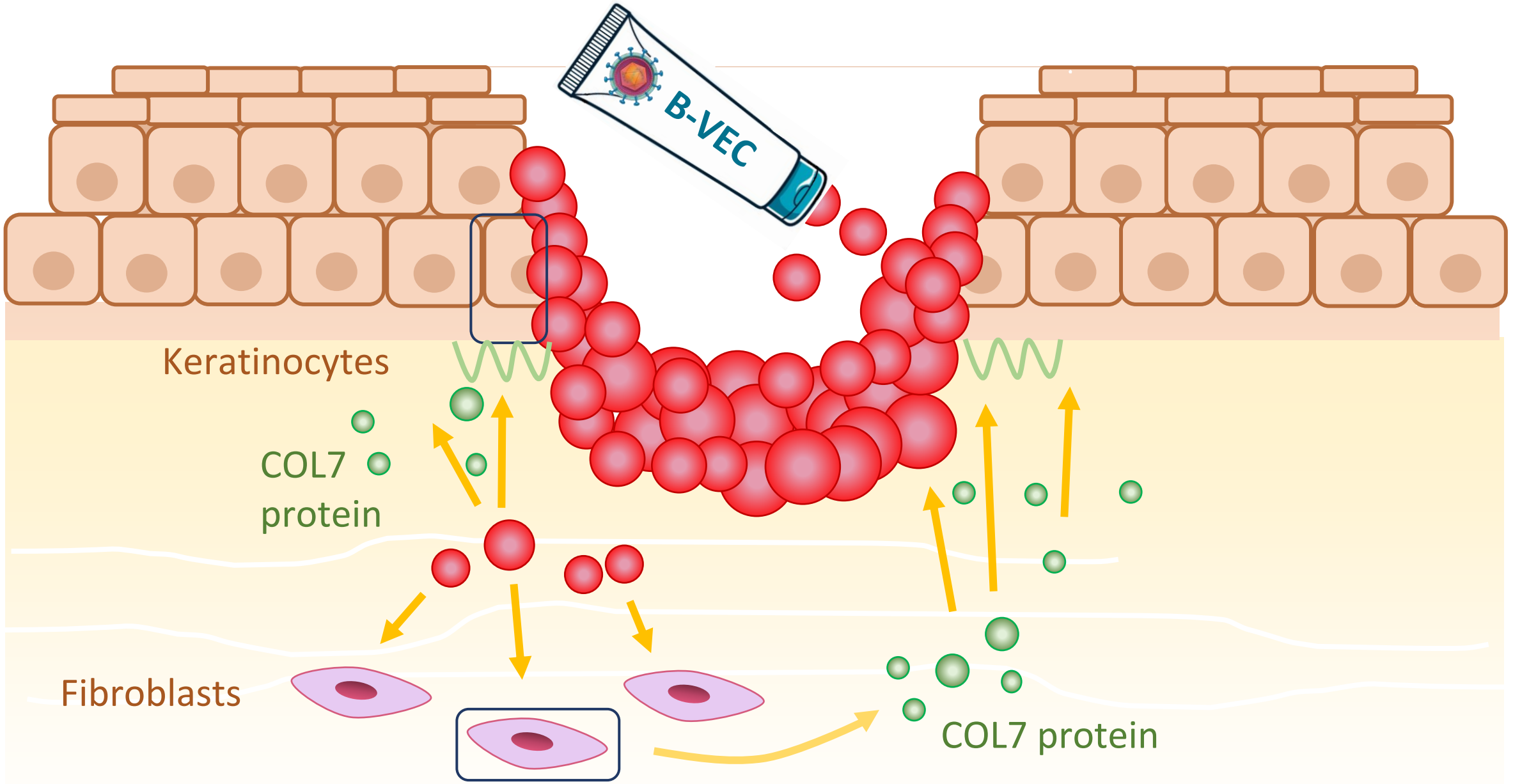
References: 1. Fine JD, Johnson LB, Weiner M et al. Epidermolysis bullosa and the risk of life-threatening cancers: the national EB registry experience, 1986–2006. J Am Acad Dermatol 2009; 60:203–11 (2). Hou et al., Intravenously Administered Recombinant Human Type VII Collagen Derived from Chinese Hamster Ovary Cells Reverses the Disease Phenotype in Recessive Dystrophic Epidermolysis Bullosa Mice. J. Investigative Dermatology 2015 135, 3060-3067

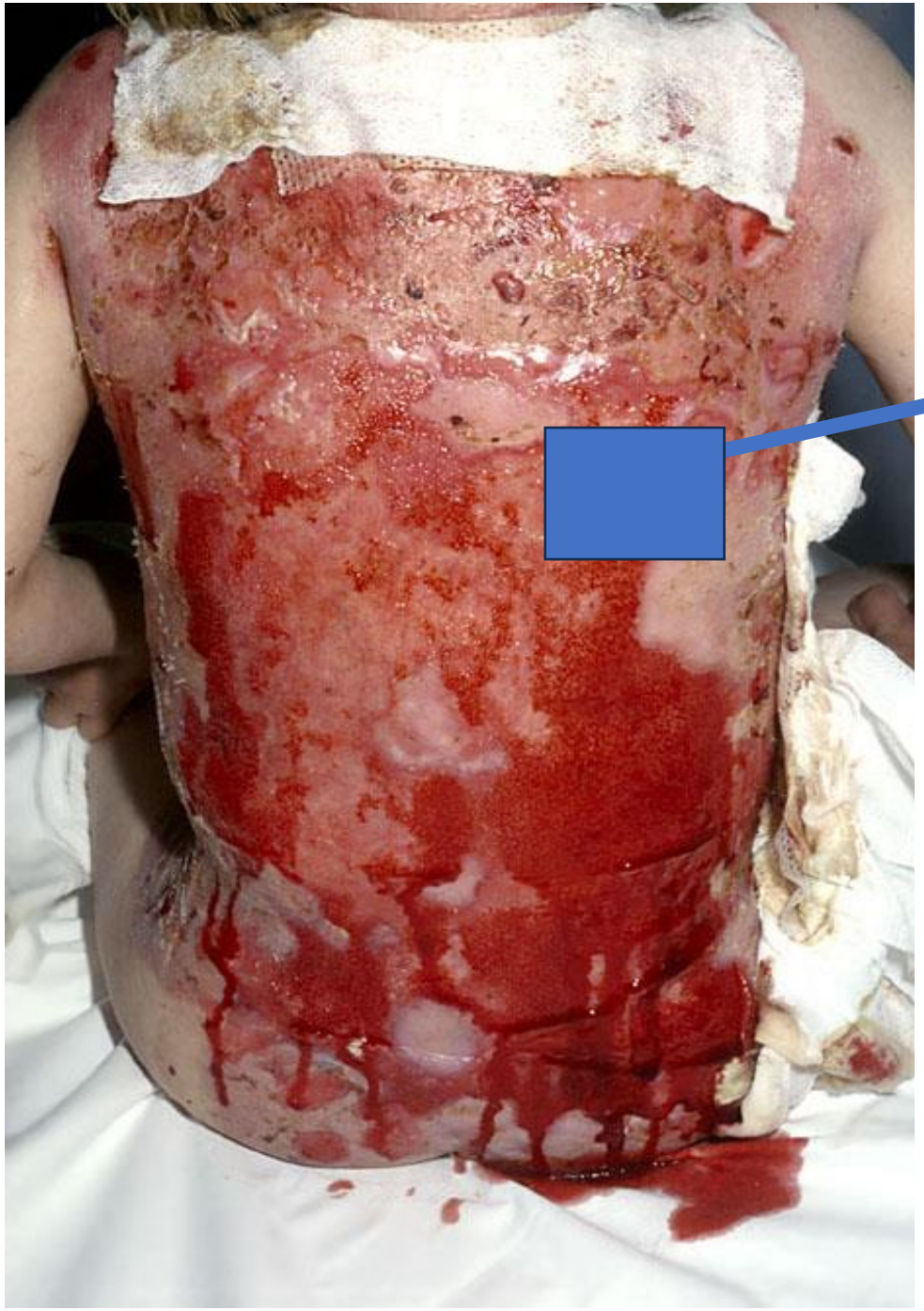
Possible value for lymphoid extracellular matrix?

Society of Pediatric Dermatology 2020

The big story for 2023/24…

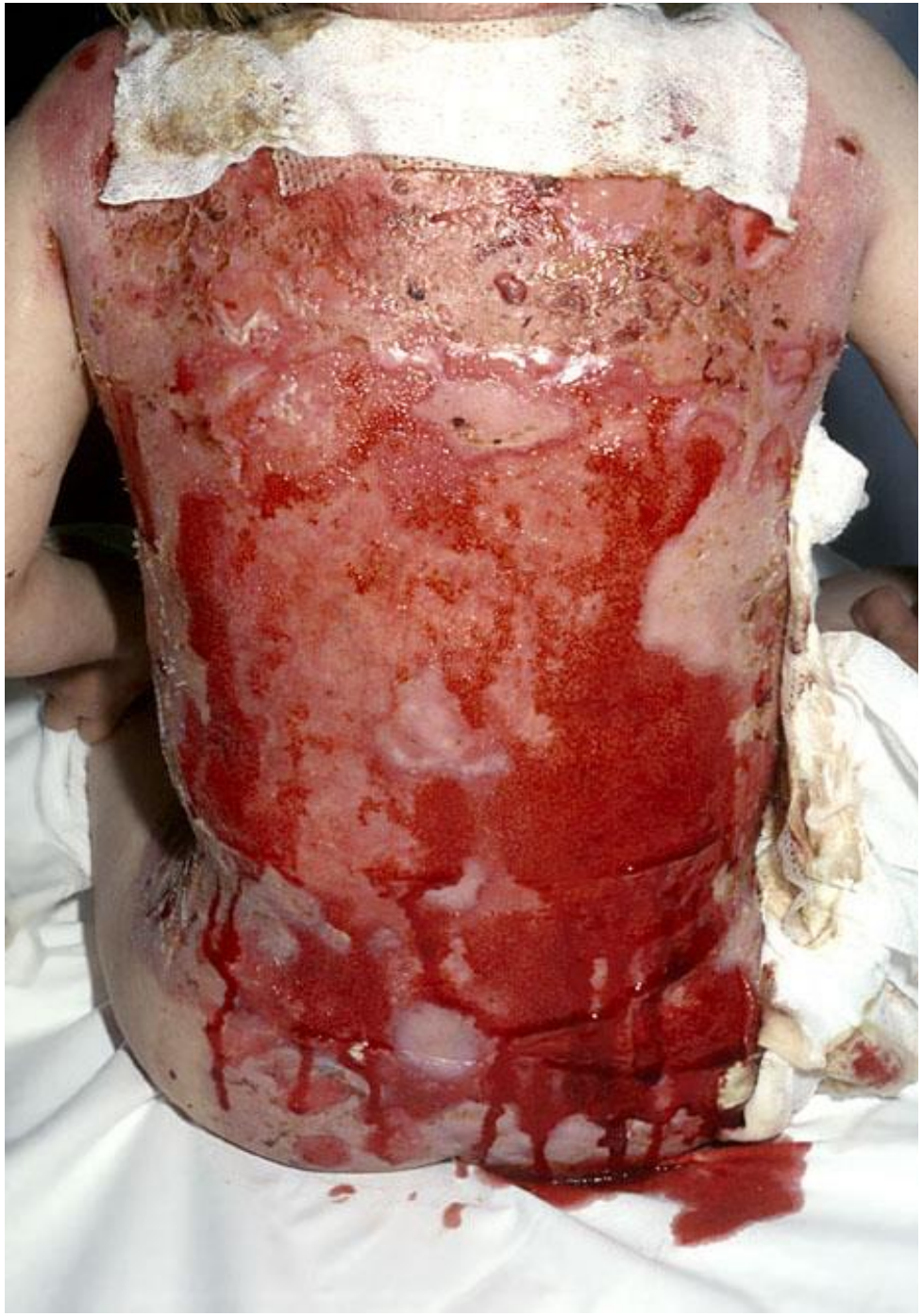
HSV-*COL7A1* gene therapy


B-VEC
Keratinocytes
COL7
protein
Fibroblasts
COL7 protein



You can only treat this small amount of eroded skin in one treatment

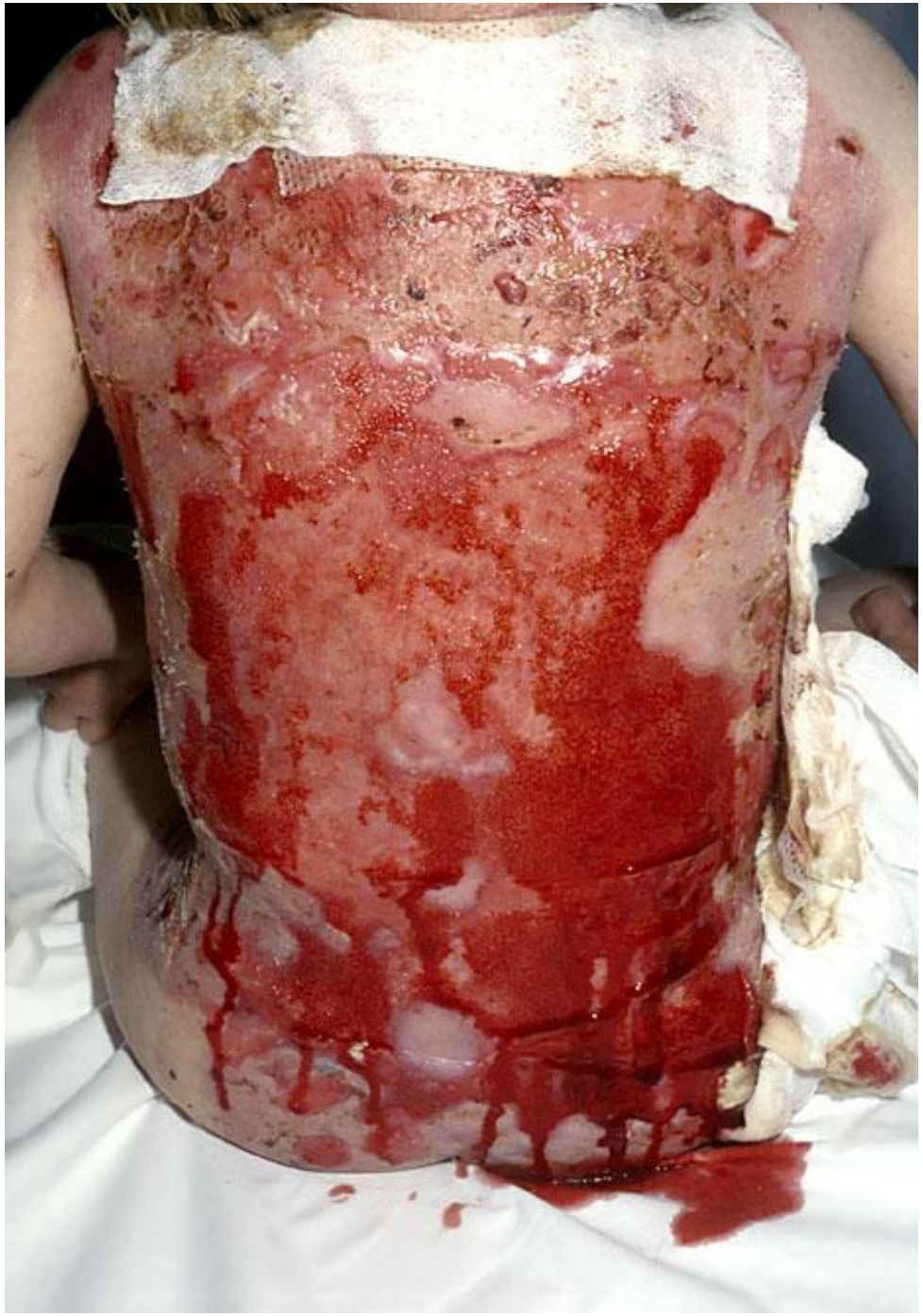
B-VEC/Vyjuvek eye drops may be helpful (but need clinical trials)



How realistic is Gene Therapy for EB?

There will be other HSV gene therapies in 2-3 years – topical and possibly systemic (via liver)

Other viruses (integrating) for gene replacement are being evaluated (*COL7A1*, *LAMB3*, *COL17A1*)

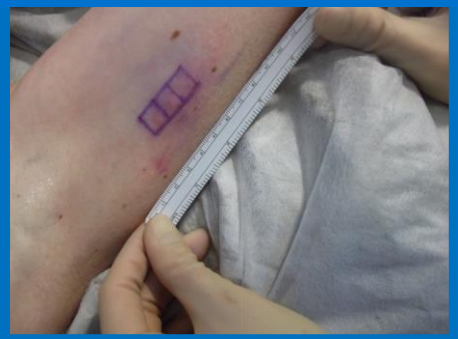


How realistic is Gene Therapy for EB?

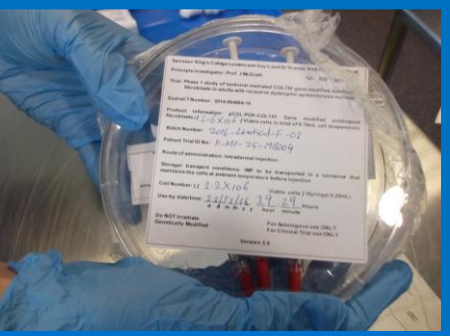
Gene editing technologies are advancing but making sure they are safe is delaying use in clinic

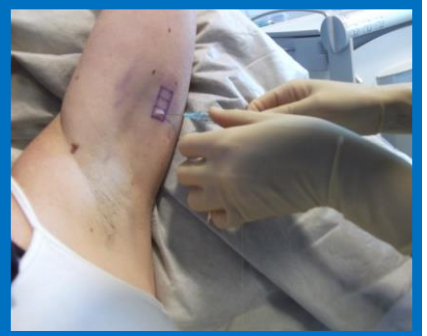
Modifying genes by inducing exon skipping is also work in progress

Stabilizing RNA with Gentamicin?

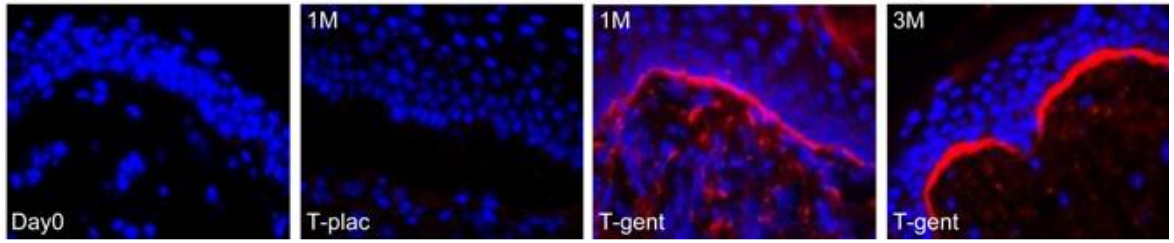
Nonsense Readthrough Therapy



Gentamicin – as a form of gene therapy

TOPICAL 0.1%



Restoration of type VII collagen in RDEB

Woodley *et al.* J Clin Invest 2017

Has *et al.*
Br J Dermatol 2020

HARD TO FIX A FAULTY GLASS OR BAD MILK

PERHAPS EASIER TO TRY TO STOP THE GLASS FALLING OR TO MOP UP THE MILK

Has *et al.*
Br J Dermatol 2020


All types of EB are associated
with some type of inflammation
Has *et al.*
Br J Dermatol 2020

FILSUVEZ

Amryt/
Chiesi

90% sunflower oil
10% birch bark extract

Anti-inflammatory

Anti-microbial

Increase keratinocyte migration

Increase keratinocyte differentiation

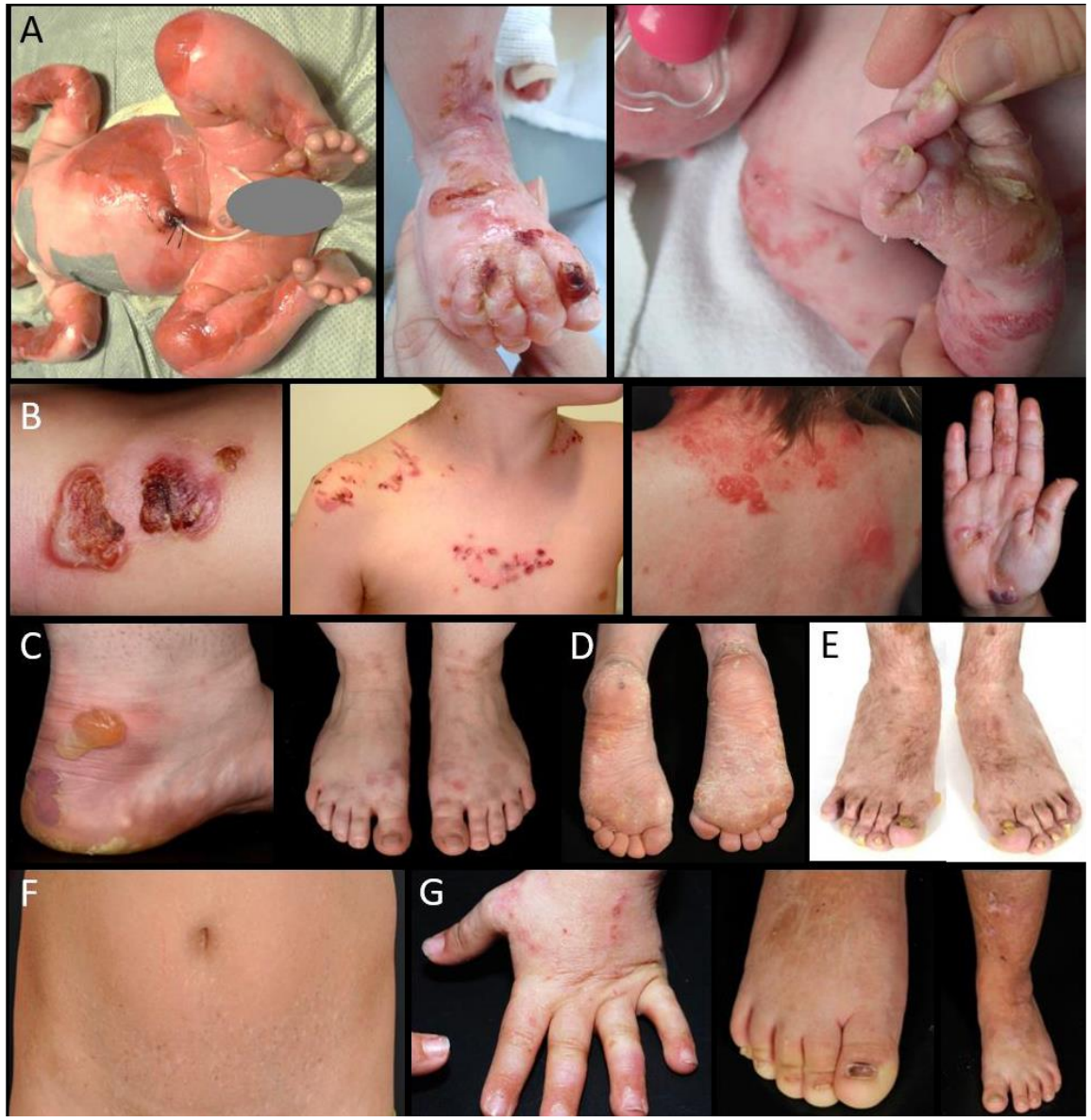
FILSUVEZ

Amryt/
Chiesi

Clinical trial data

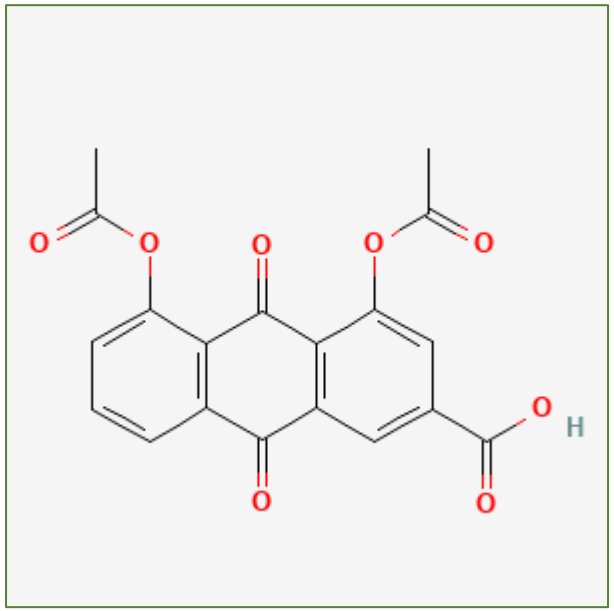
Real world experience

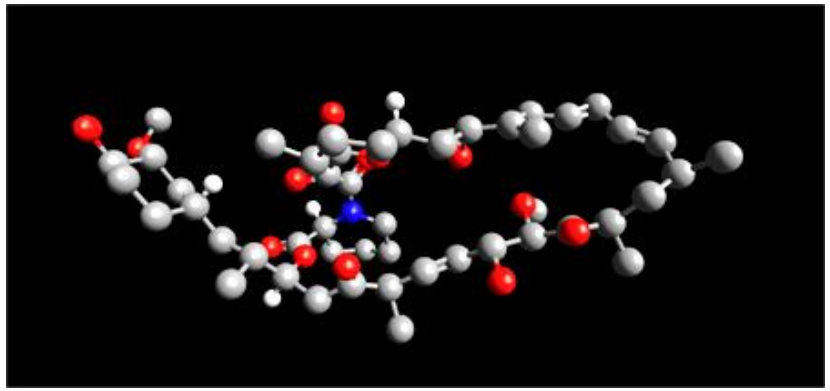
EB SIMPLEX



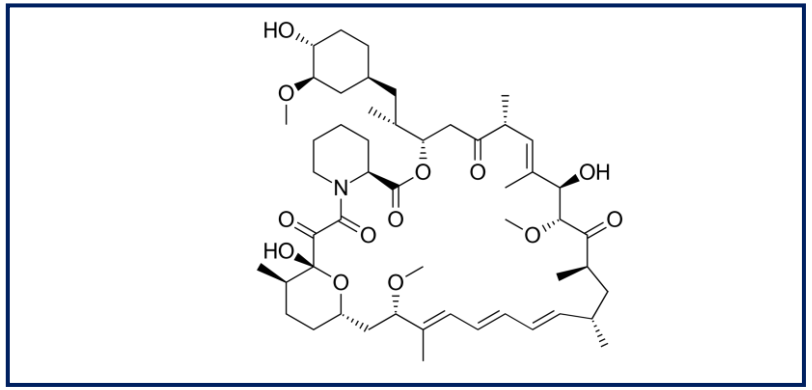
IL1β

Diacerin





Topical 2% Sirolimus in EB Simplex



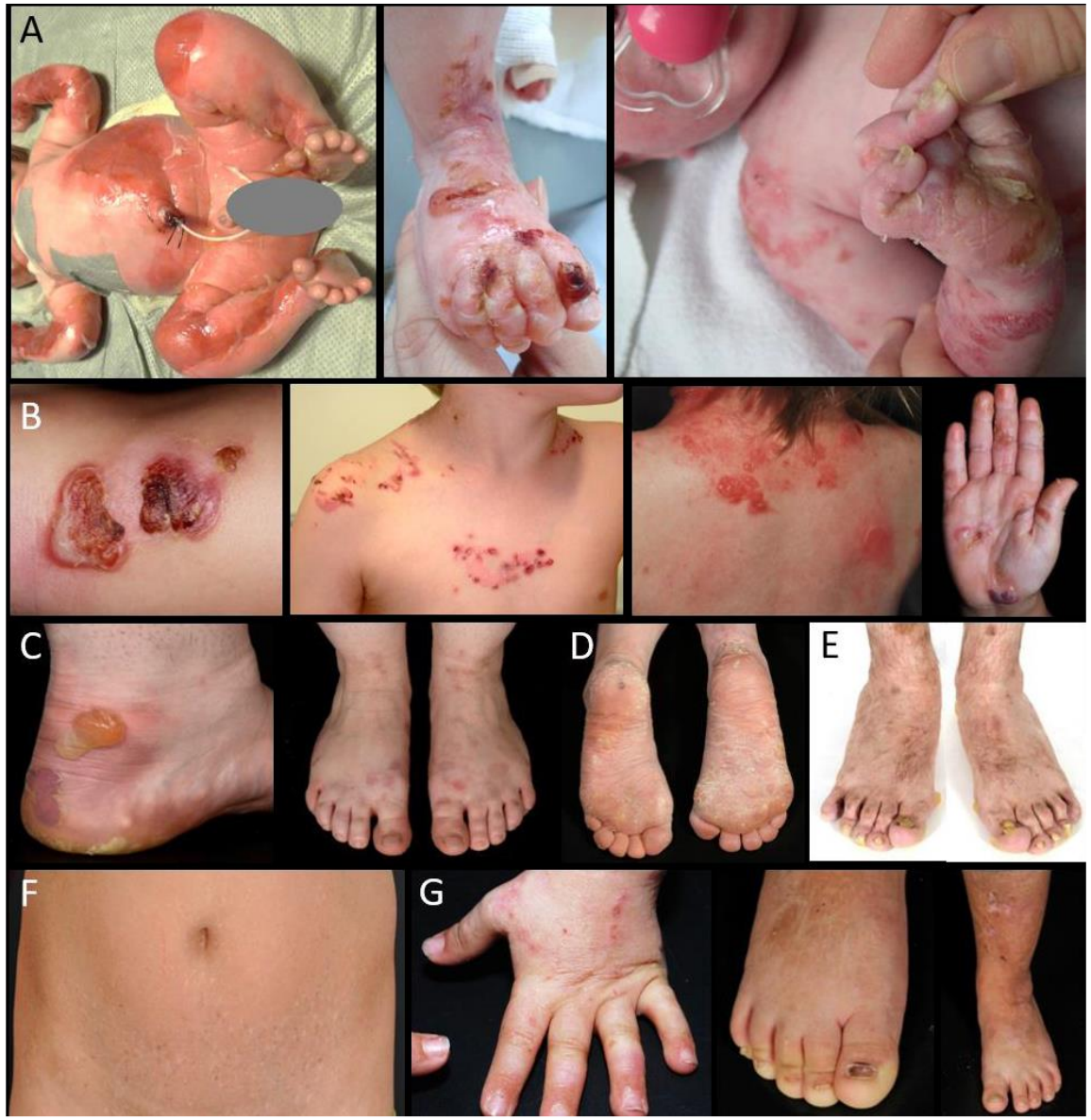
PI3K/Akt/mTOR signalling pathway activation

Topical 2% sirolimus
(also known as rapamycin, a potent mTOR inhibitor)

Two patients reported significant clinical improvement, with reduced blistering and keratoderma, improved walking, and reduced foot pain after 12 weeks of treatment

Lee et al.
J Invest Dermatol 2022

EB SIMPLEX

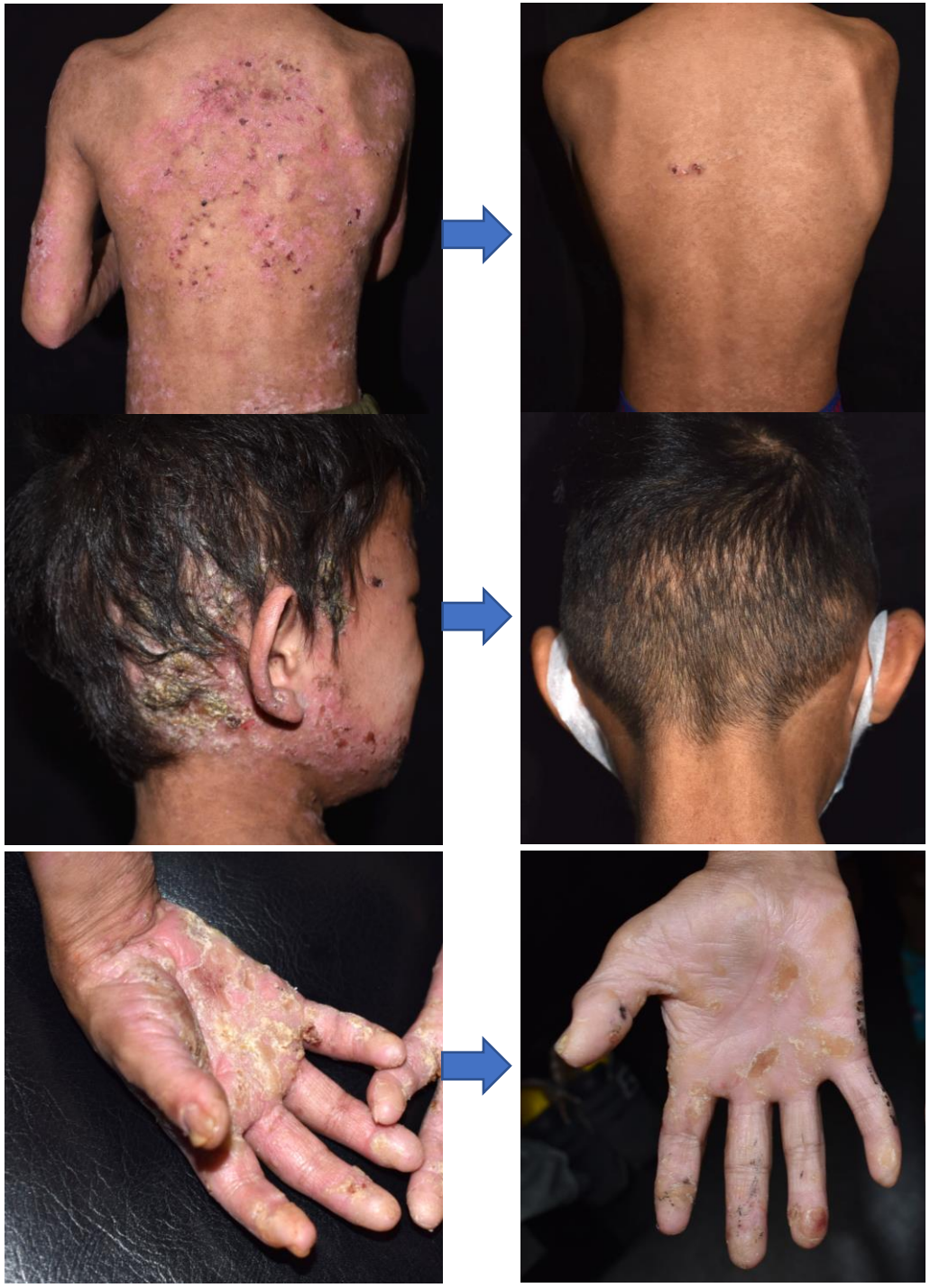


Thymosin β4

Apremilast

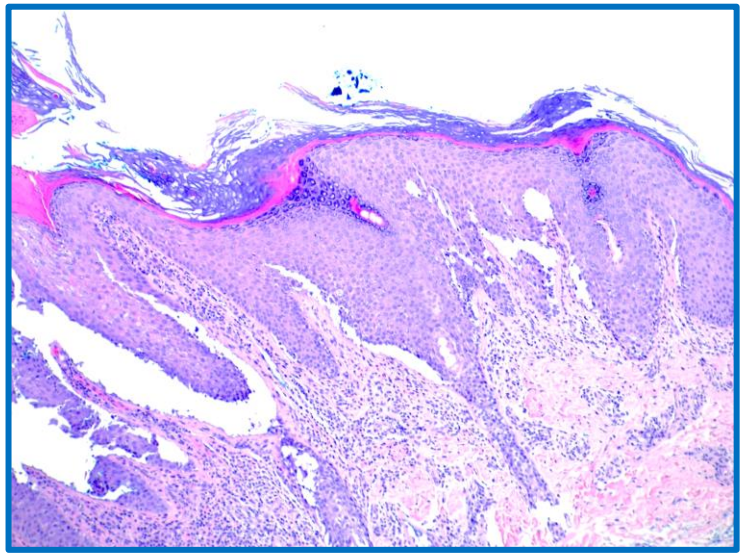
Tetracycline

Before treatment



After treatment

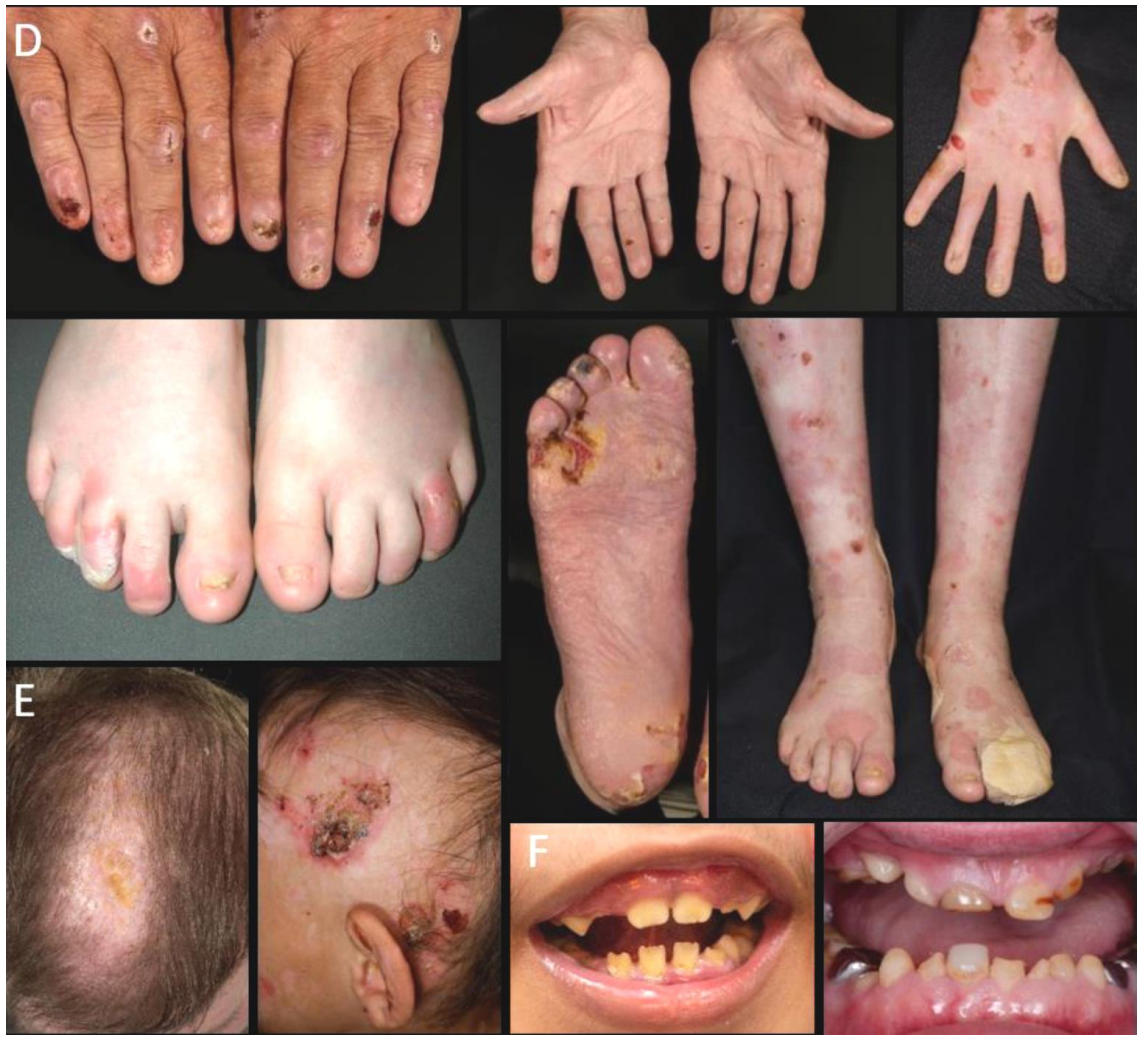
Ivermectin



EB simplex with Scabies

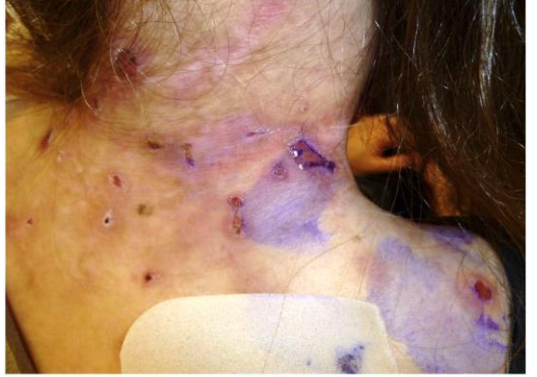
Lin et al.
J Dermatol 2022

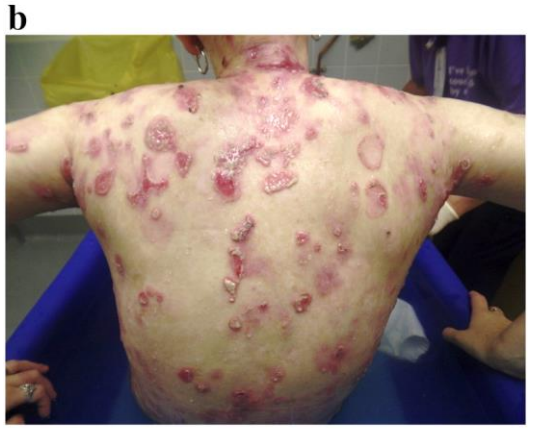
JUNCTIONAL EB

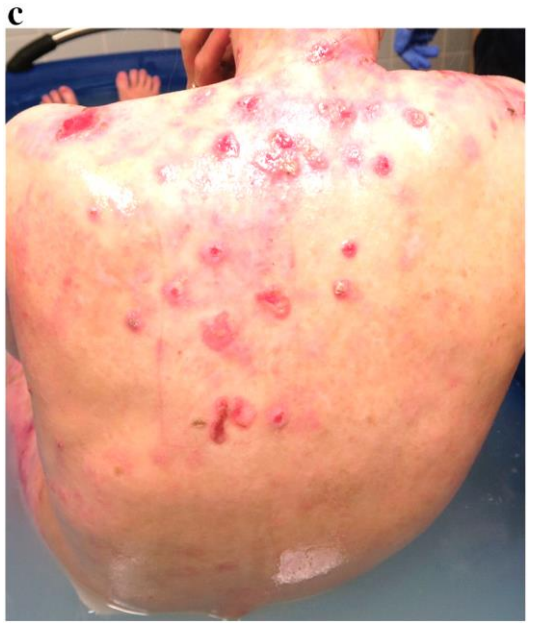


Clinical reduction in granulation tissue using oral colchicine

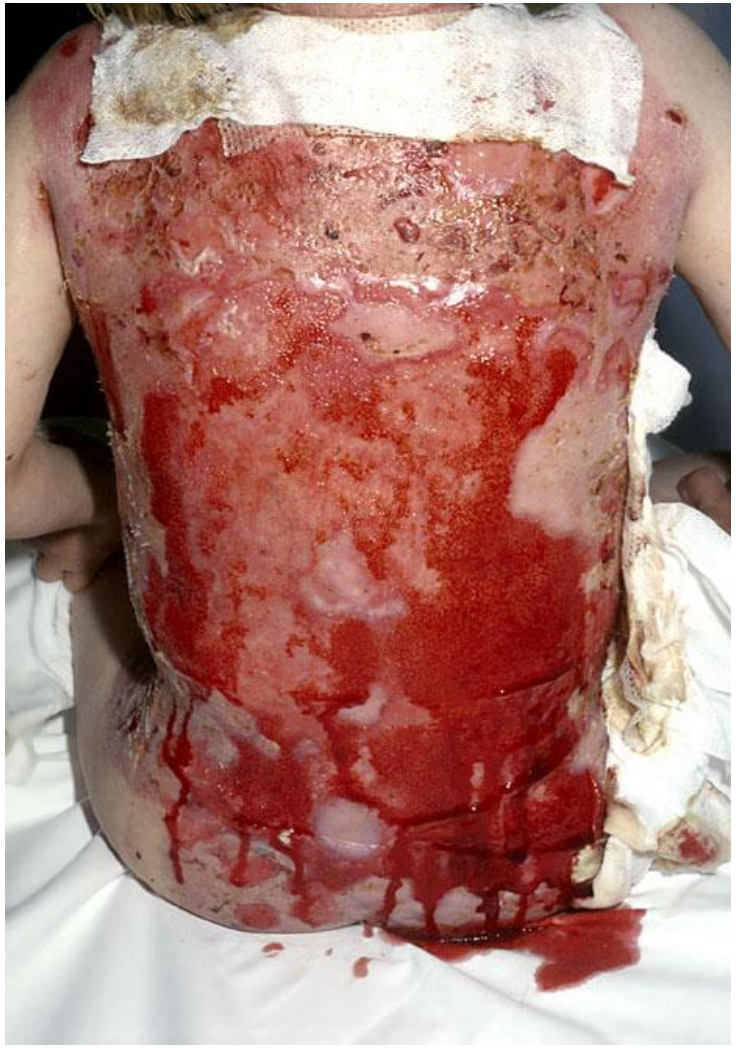
Kim *et al.*
Int J Womens Dermatol
2016





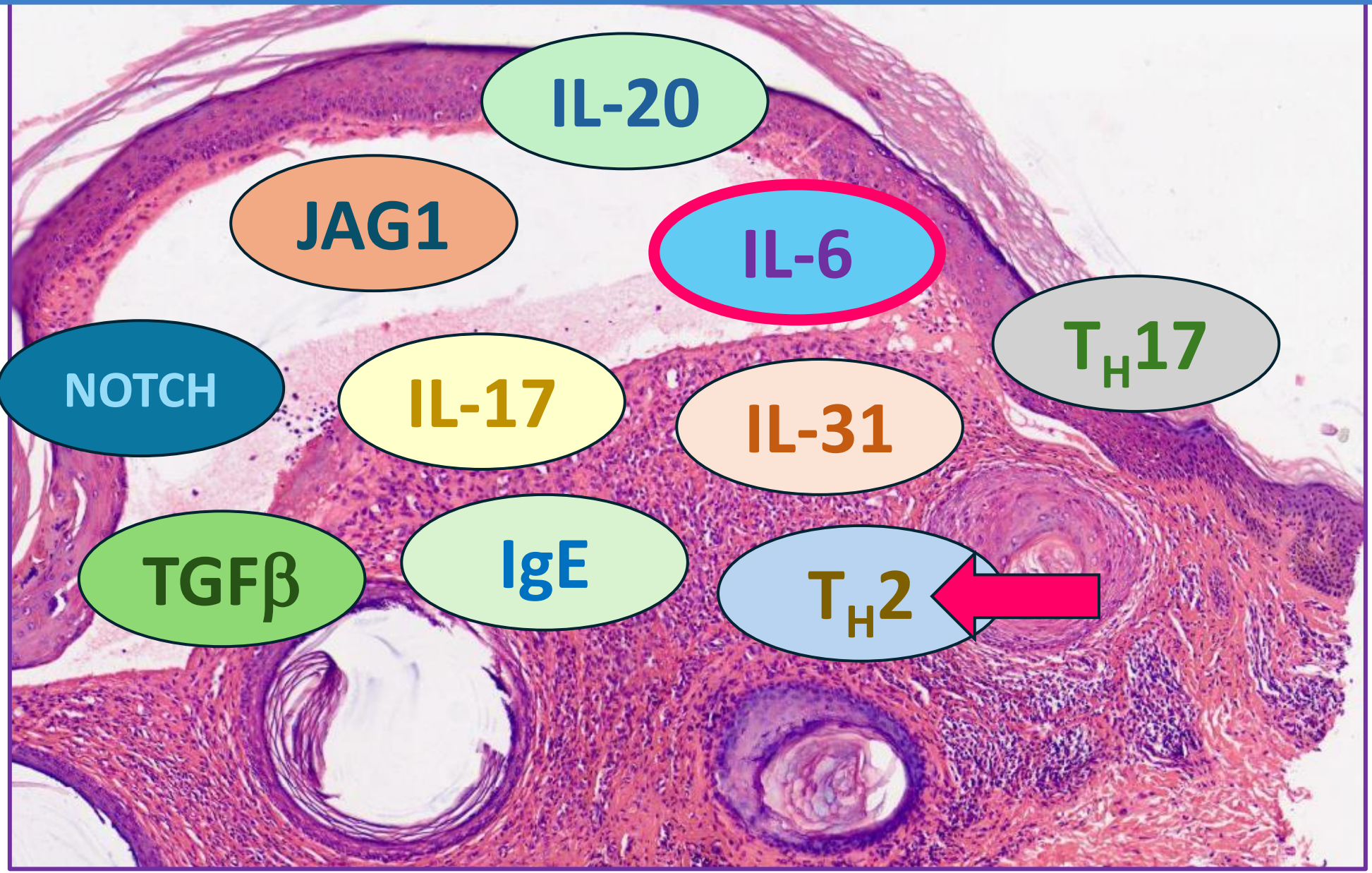


(SEVERE) DYSTROPHIC EB



Refinement of inflammatory profiling through **multi-omic data**...

DEB is an INFLAMMATORY disease: with identifiable targets



Histology image:
Hassan
Vahidnezhad

Br J Dermatol 2024; **191**:252–260
https://doi.org/10.1093/bjd/ljae110
Advance access publication date: 13 March 2024

BJD
British Journal of Dermatology
Translational Research

Dominant dystrophic epidermolysis bullosa is associated with glycolytically active *GATA3*$^+$ T helper 2 cells which may contribute to pruritus in lesional skin

Wilson Jr F. Aala,[1] Ping-Chen Hou,[2] Yi-Kai Hong,[2,3] Yu-Chen Lin,[2,3] Yu-Rong Lee,[4] Wei-Ting Tu,[2] Marieta Papanikolaou,[5] Natashia Benzian-Olsson,[5] Alexandros Onoufriadis,[5,6] Hans I.-Chen Harn,[7] Daw-Yang Hwang,[8] Siao Muk Cheng,[8] Kurt Lu,[9] Peng-Chieh Chen,[1] John A. McGrath[4,5] and Chao-Kai Hsu[1,2,3]

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Correspondence: Chao-Kai Hsu. Email: kylehsu@mail.ncku.edu.tw

Linked Article: Samuelov *Br J Dermatol* 2024; **191**:159–160.

Abstract

Background Dominant dystrophic epidermolysis bullosa (DDEB) is characterized by trauma-induced blisters and, in pruritus. Precisely what causes itch in DDEB and optimal ways to reduce it have not been fully determined.

Objectives To characterize DDEB skin transcriptomes to identify therapeutic targets to reduce pruritus in patien

Methods Using bulk RNA sequencing, we evaluated affected and unaffected skin biopsy samples from six pati very itchy pruriginosa subtype) and four healthy individuals. Single-cell transcriptomes of affected ($n=2$) and una healthy skin ($n=2$) were obtained. Dupilumab treatment was provided for three patients.

Results The skin bulk transcriptome showed significant enrichment of T helper (Th)1/2 and Th17 pathways in a with nonlesional DDEB skin and healthy skin. Single-cell transcriptomics showed an association of glycolytical affected DDEB skin. Treatment with dupilumab in three people with DDEB led to significantly reduced visual ana after 12 weeks (mean VAS 3.83) compared with pretreatment (mean VAS 7.83). Bulk RNAseq and quantitativ showed that healthy skin and dupilumab-treated epidermolysis bullosa (EB) pruriginosa skin have similar transcri Th1/Th2 and Th17 pathway enrichment.

Conclusions Single-cell RNAseq helps define an enhanced DDEB-associated Th2 profile and rationalizes drug rep in treating DDEB pruritus.

Lay summary

Dominant dystrophic epidermolysis bullosa (DDEB) is a rare inherited skin disease that causes fragile skin that blisters easily gered by minor injuries. These blisters are accompanied by intense itching, which can be distressing. The underlying cause of D in genetic mutations in a gene called *COL7A1*. This gene encodes 'type VII collagen', a protein crucial for attaching the outer skin la (epidermis) to the layer beneath (dermis).

Although the genetic basis of DDEB is understood, the causes of itch are not known. As well as this, effective treatments for DDEB are lacking, which has driven scientists to explore innovative approaches like repurposing existing drugs. Drug repurposing involves using medications that have already been approved for other health conditions. One such drug is dupilumab, which is used for severe atopic

Accepted: 8 March 2024

DEB-P inflammation is confined to lesional skin

JAAD
Journal of the American Academy of Dermatology

Th2 response drives itch in dystrophic epidermolysis bullosa pruriginosa: A case-control study

To the Editor: Itch is the commonest skin complaint, and it is highly prevalent in the inherited blistering condition dystrophic epidermolysis bullosa (DEB).[1] However, research into itch mechanisms beyond common skin conditions remains sparse. We conducted a case-control study aiming to elucidate molecular itch mechanisms in

the extremely itchy DEB subtype known as DEB riginosa (DEB-P).[2]

anikolaou, MBBS, PhD,[a] Leigh PhD,[b] Natashia Benzian-Olsson, PhD,[c] Alyson Guy,[c] Han Lu, Kadiyirire, MRes, BSc,[a] Ping- D,[e] Wilson Aala, MSc,[f] Sonia Rashida Pramanik, BSc,[g] Nina Konstantina Dimitrakopoulou, n, MBBS, PhD,[a] Emily Kalfas,[a] MSc,[h] Roman Laddach, MRes,[a] Cozzetto, PhD,[g] Bjorn Thomas, D,[i] Evangelia Kesidou, PhD,[a] Ellie amat, MBBS, PhD,[a] Guy Orchard, Edel A. O'Toole, MB, BCh, PhD,[i] Chao- Hsu, MD,[e,f,j] Mansoor Saqi, PhD,[g] Martin Steinhoff, MD, PhD,[k] Alexandros Onoufriadis, PhD,[a,l] Gil Yosipovitch, MD,[b] Hannah Gould, BA, PhD,[m] Jemima E. Mellerio, MBBS, MD,[a] and John A. McGrath, MBBS, MD[a]

J Am Acad Dermatol
Volume 91, Number 1

2024, pp131-133

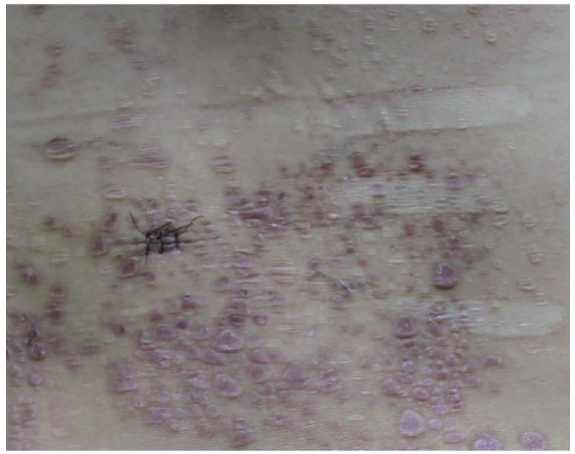
Drugs like dupilumab can help the itch

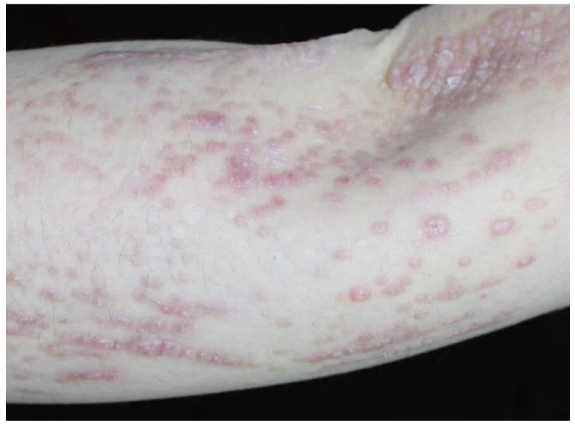
in some forms of dystrophic EB

Zhou et al. *Ped Dermatol* 2021

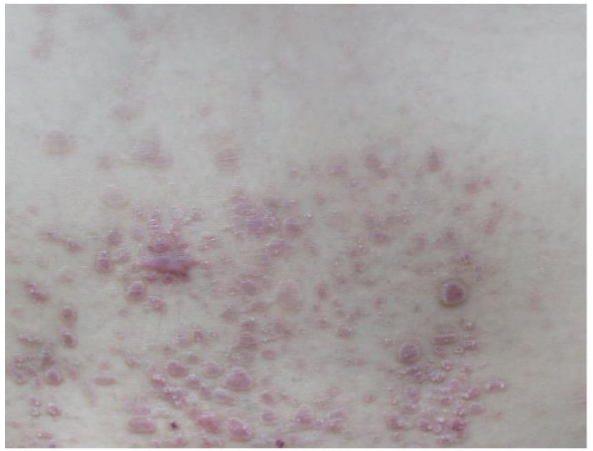
Itchy forms of dystrophic EB may also improve after oral Tofacitinib (JAK1/2 inhibition)

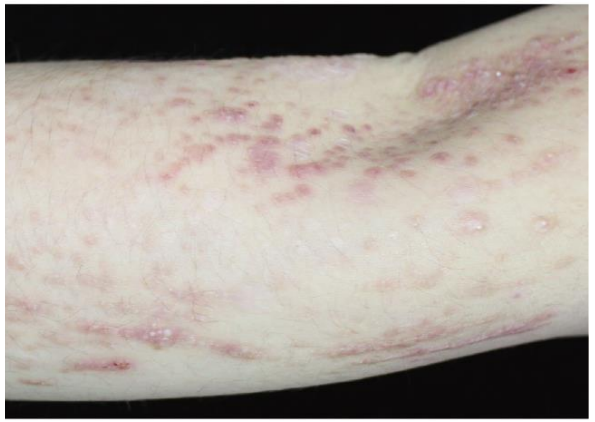
Before



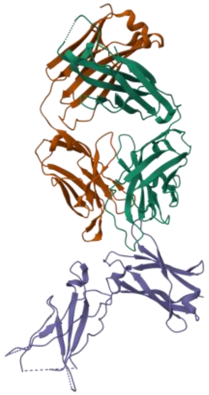


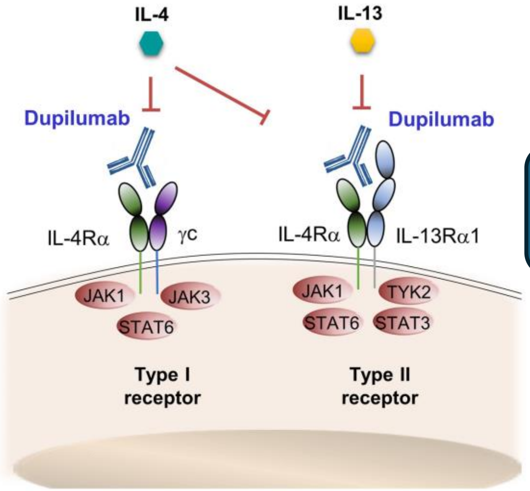
After 4 weeks (5 mg bd)





Chen et al.
Clin Exp Dermatol
2021






DOI: 10.1002/ski2.445

RESEARCH LETTER

SKIN HEALTH AND DISEASE

Real-world experience of using dupilumab and JAK inhibitors to manage pruritus in epidermolysis bullosa pruriginosa

Dear Editor,
Epidermolysis bullosa pruriginosa (EBP) is a form of dystrophic EB characterised by prurigo-like nodules. It is associated with severe pruritus[1] and exhibits skewed Th2 inflammation in both blood and lesional skin.[2] Controlling itch in EBP is a major clinical challenge.
Over the last 4 years, anecdotal reports and sm
series have highlighted the value of ei
ous dupilumab or oral Janus kin
baricitinib, upadacitinib and tof
itch and improving the pati
the current literature lac
tween the two treatm
changes following JA
mented to date. Here
both types of trea
(Supplementary Ta
data in EBP skin
Following the
the beneficial imp
patients with EB
dupilumab (300 m
up to 14 months (
treatment and pos
(NRS) were 7 (6.5–
The overall clinical
(Figure 1a). Moreove
in 2 further subjects wi
response (see below a
Based on the experience o
JAKi in EBP, we treated 3

60 years) who had shown minimal response to dupilumab with JAKi. One patient had responded poorly to 4 doses of dupilumab (itch NRS: 9→8) and was changed

to abrocitinib 200 mg/day for 1 month initially, subsequently reduced to 100 mg/day for a further 3 months, with a much better response (itch NRS: 7→0). The other patient initially had a good response following 3 months of dupilumab treatment (itch NRS: 8.5→3.5) but relapsed thereafter. She was re-treated with dupi-
with minimal response (given 7 months after the
NRS: 6→5). She then changed to upa-
orally for 9 months with a major
itch NRS: 5→0). The prurigo le-
ed in number and were less
One further EBP patient
mptom relief after dupilu-
available itch NRS) but
d 1 year later with itch
mg/day orally was
response (itch NRS:
Collectively, 6 pa-
d JAKi in our study.
ients with available
0% reduction in itch
te relief (NRS = 0).
available itch scores
and Supplementary
e patient experienced
nd one had a slightly
dacitinib but no major
No adverse events were
rm.
scriptomic changes following
skin and peripheral blood using

specimens were separated from the pre-treatment samples (Figure 1e). PathfindR enrichment analysis identified Th1/2 cell differentiation as the most enriched

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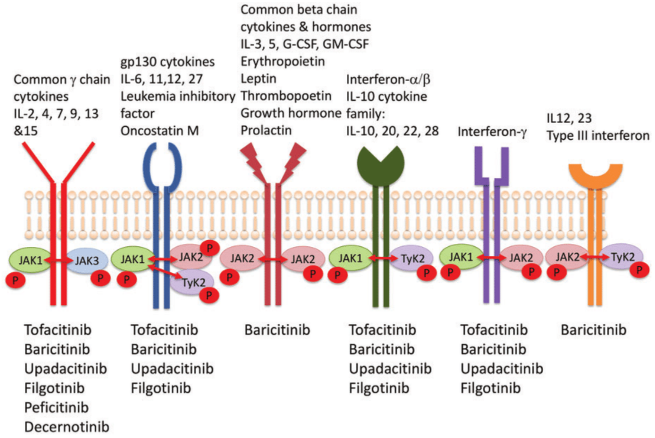
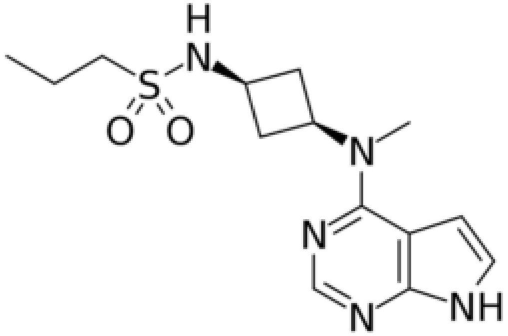
Skin Health Dis. 2024;4:e445. https://doi.org/10.1002/ski2.445 wileyonlinelibrary.com/journal/ski2 1 of 4

EB pruriginosa can also be painful

Jeffs E *et al*. Orphanet J Rare Dis 2024



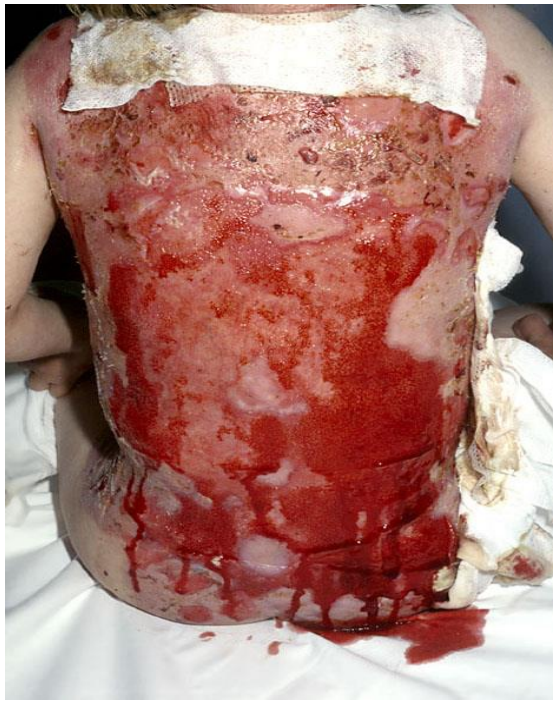


Biologics and JAKi are also expensive

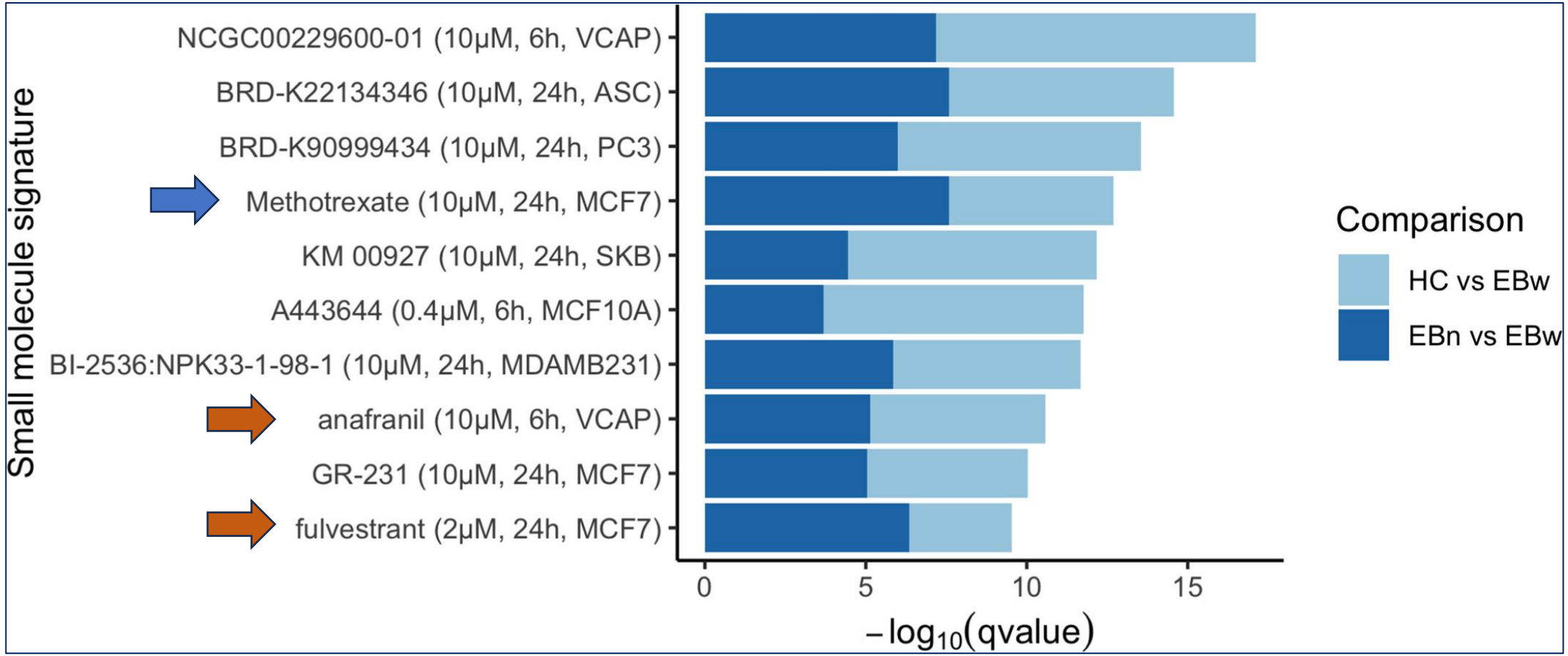
Repurposing of some cheaper drugs like

METHOTREXATE might be useful

What about re-purposing drugs to help patients with RDEB?



Onoufriadis et al.
Exp Dermatol
2022



Also on the list is SIMVASTATIN

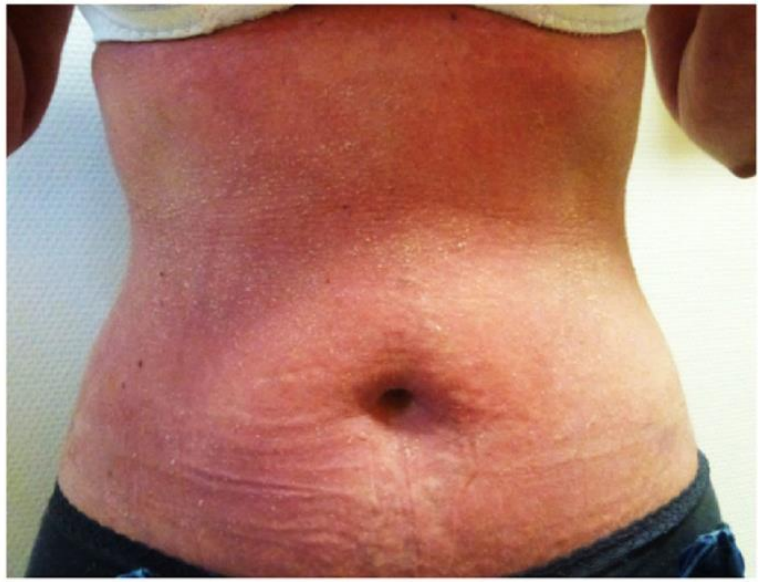
STATINS to improve wound healing in RDEB?

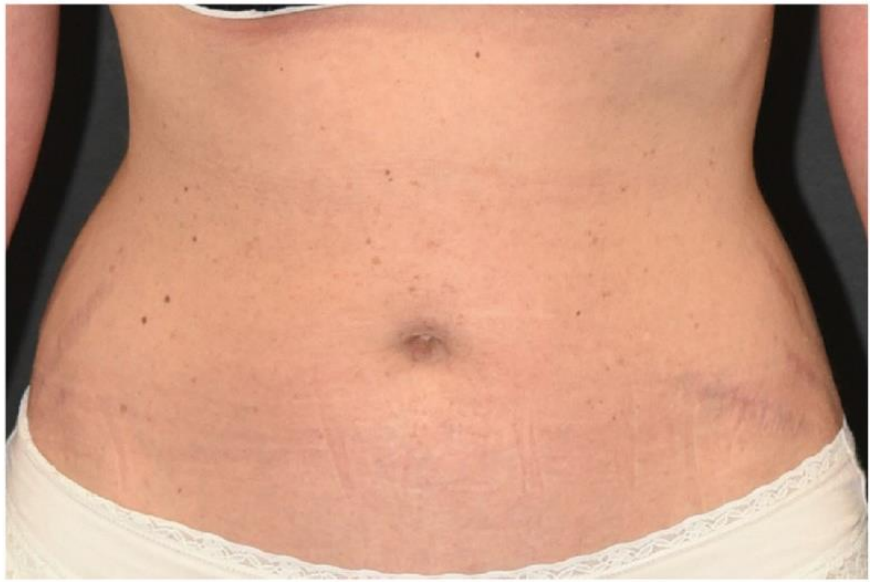
Biologics and JAKi are not included in L1000FWD reverse transcriptomics

Growing anecdotal evidence of impact of these drugs for genodermatoses

Clinical response of SAM syndrome

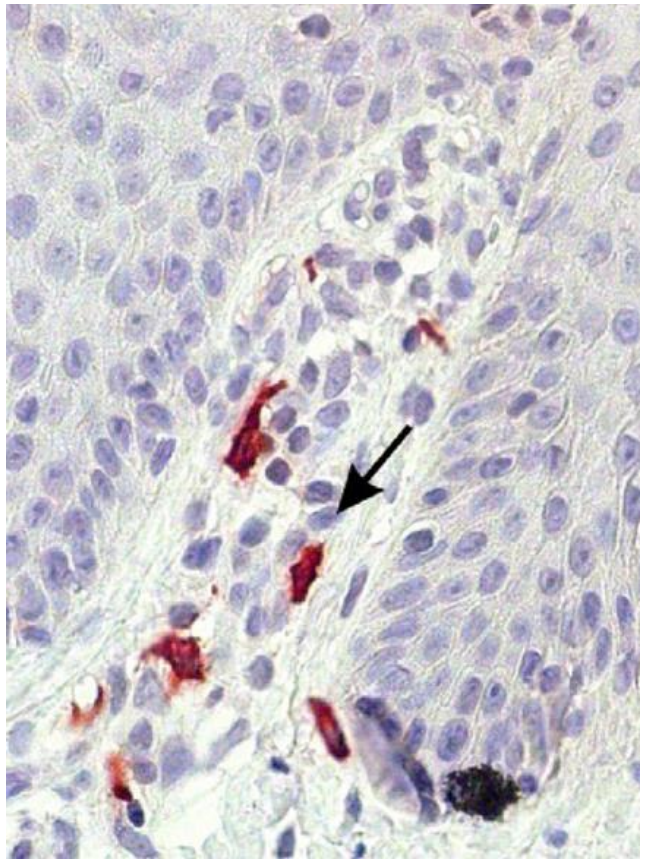
(desmoglein 1 knockout) to Secukinumab





Frommherz et al. *Br J Dermatol* 2021

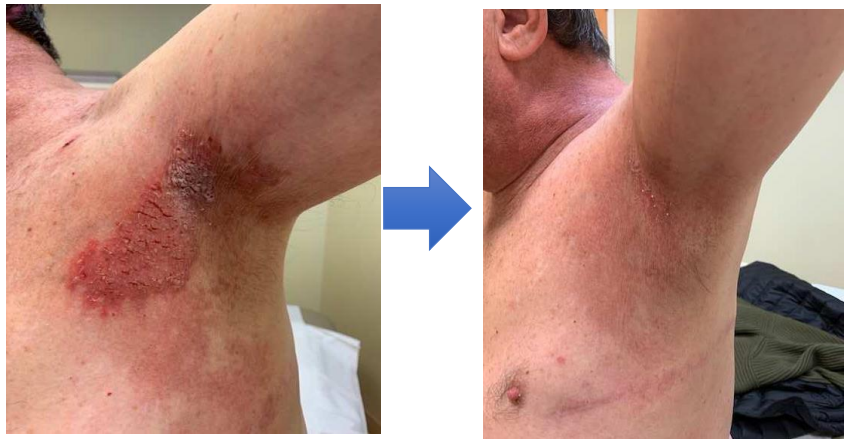
Increased IL-17
in lesional skin
pre-treatment



The era of biologics for treating EB (and other genodermatoses)?

Dupilumab for genodermatoses

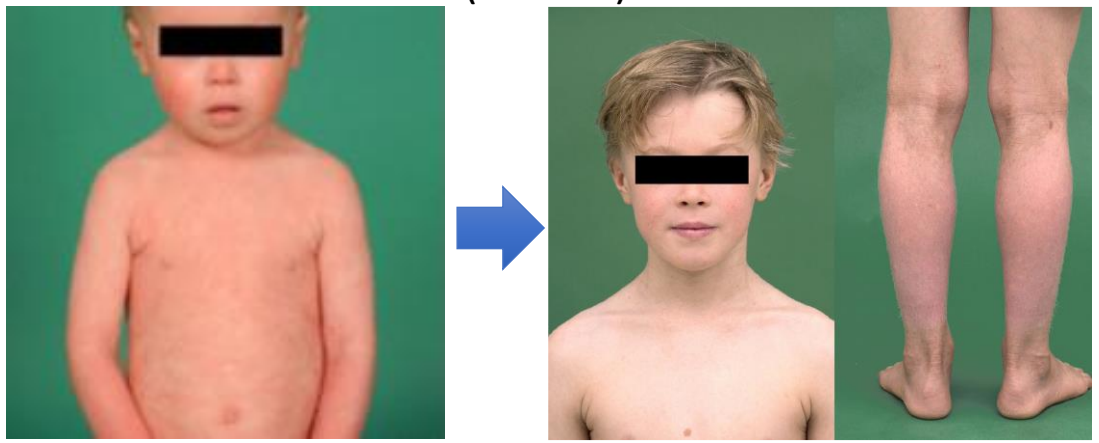
Hailey Hailey disease (*ATP2C1*)



Alzahrani et al. *Br J Dermatol* 2022

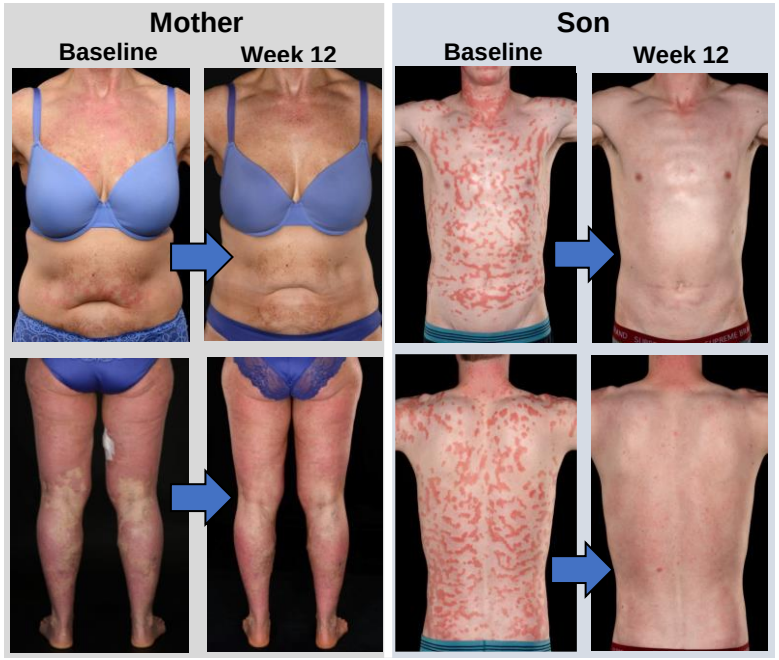
Ustekinumab for genodermatoses

ARCI (*NIPAL4*)



Poulton et al. *Ped Dermatol* 2019

PRP (*CARD14*)



Lwin et al.
Br J Dermatol 2018

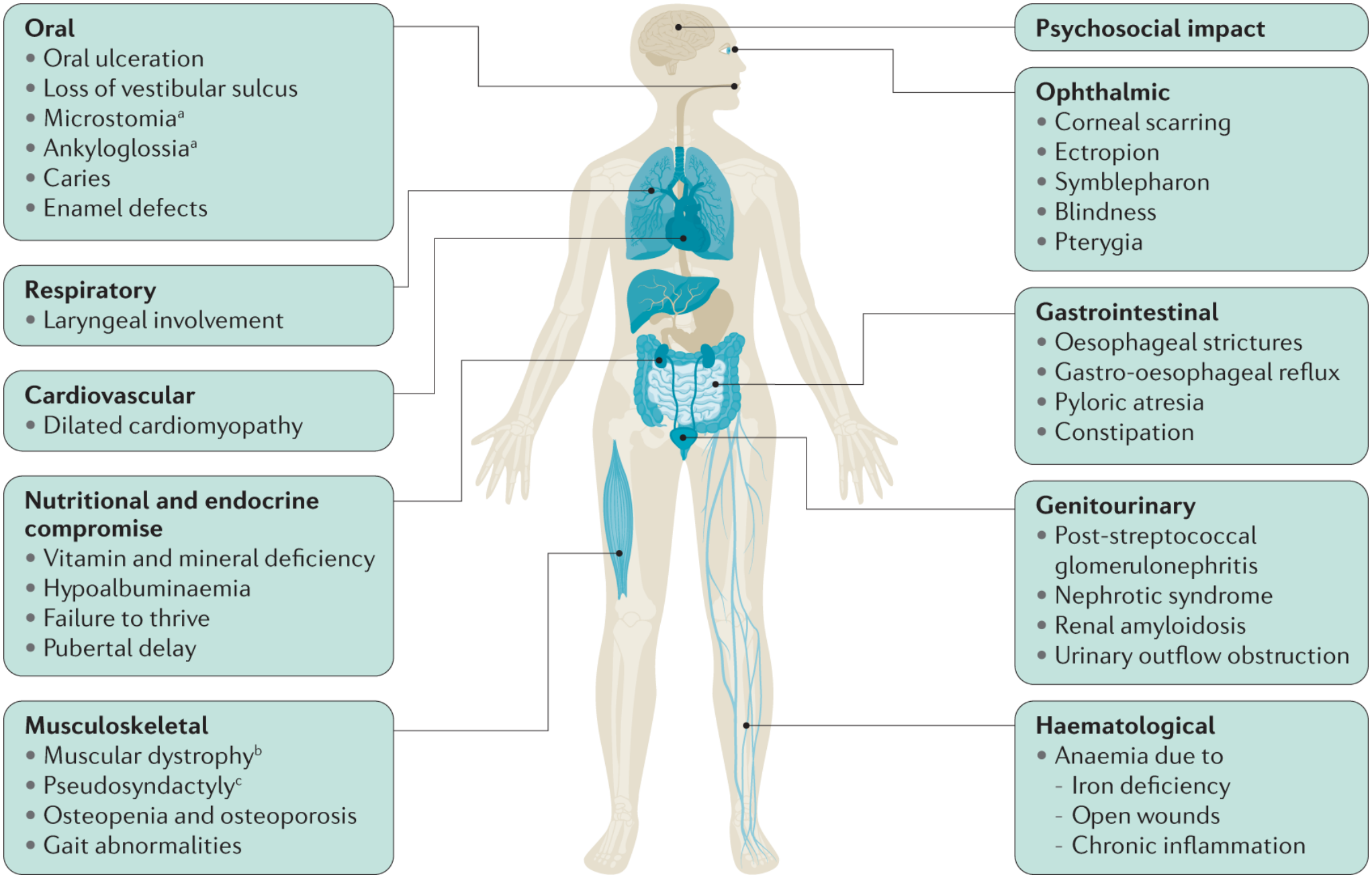
The use of biologics and JAKi for

improved symptom control

Systemic Impact

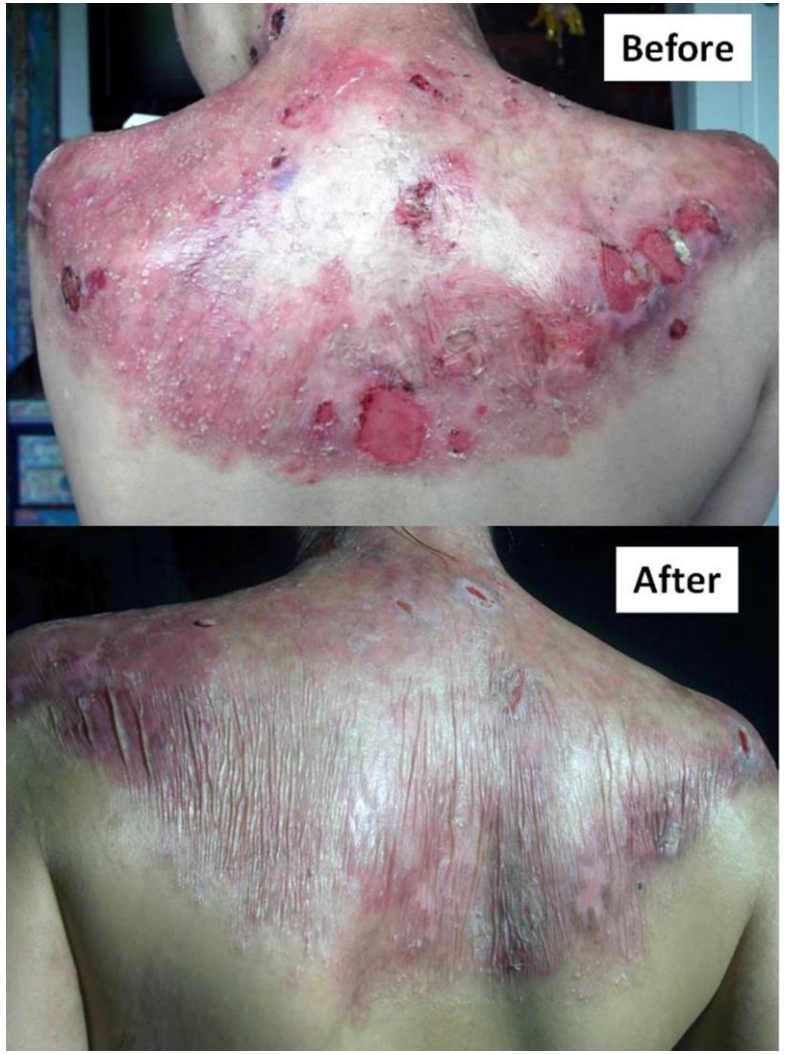
The use of biologics and JAKi to

reset readiness for other interventions



Bardhan *et al.* Nat Rev Dis Primers 2020

Intravenous allogeneic mesenchymal stromal cells for RDEB



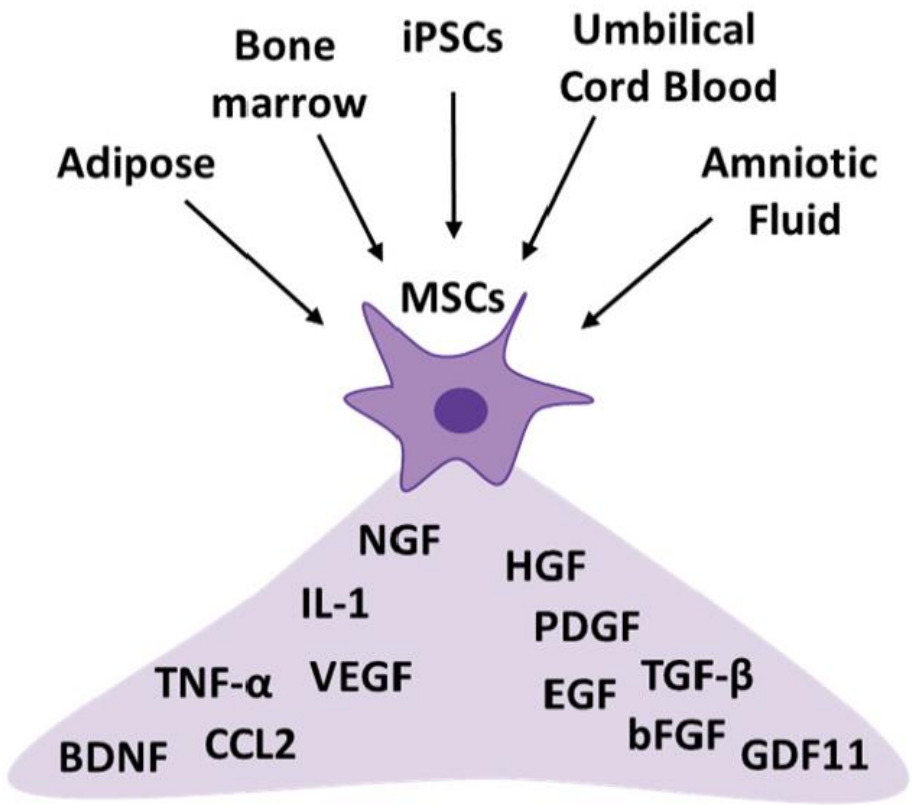
Petrof *et al.* J Invest Dermatol 2015

MISSION EB

clinical trial

RHEACELL

clinical trials

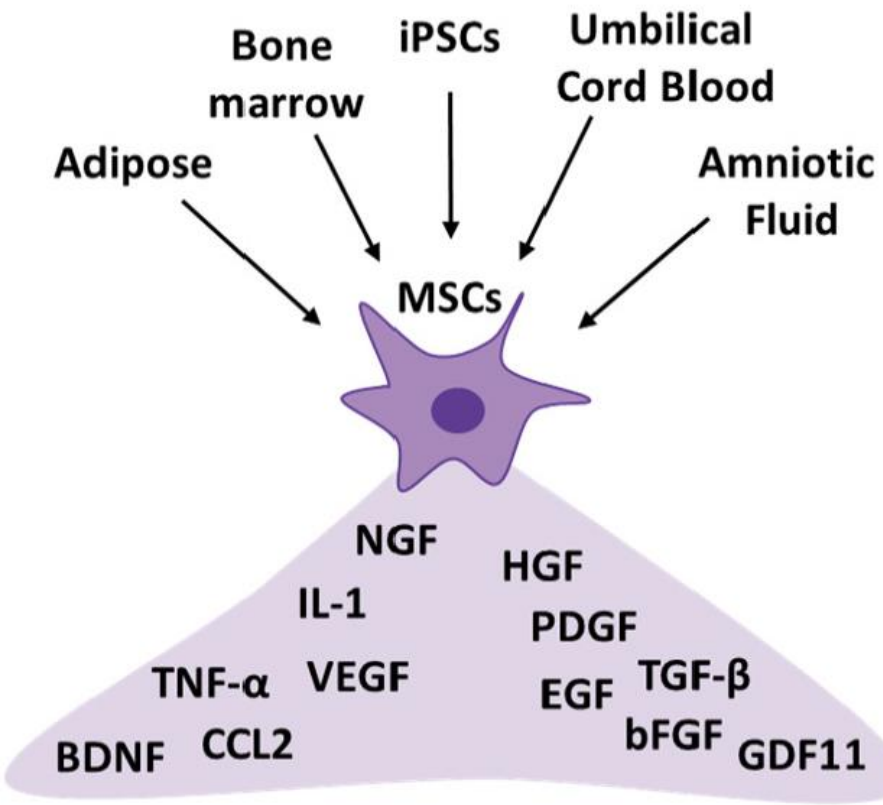


Jo *et al.* Int J Mol Sci 2021

MSCs work best in younger patients with milder disease

Pre-treatment or combination treatment with other anti-inflammatories

EXOSOMES?



Jo *et al.* Int J Mol Sci 2021

MSCs work best in younger patients with milder disease

Pre-treatment or combination treatment with other anti-inflammatories

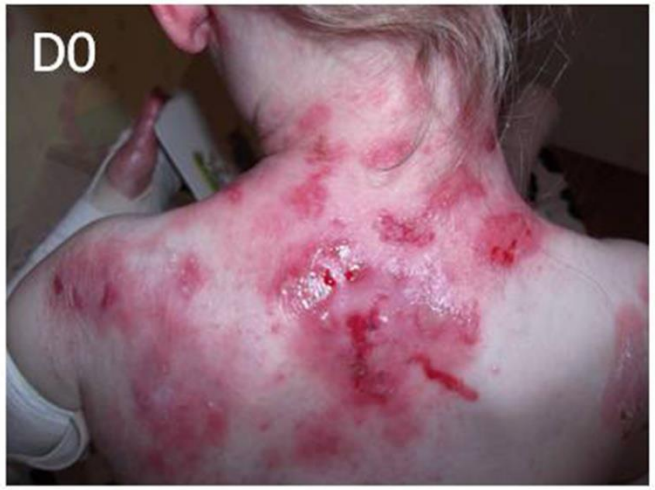
EXOSOMES?

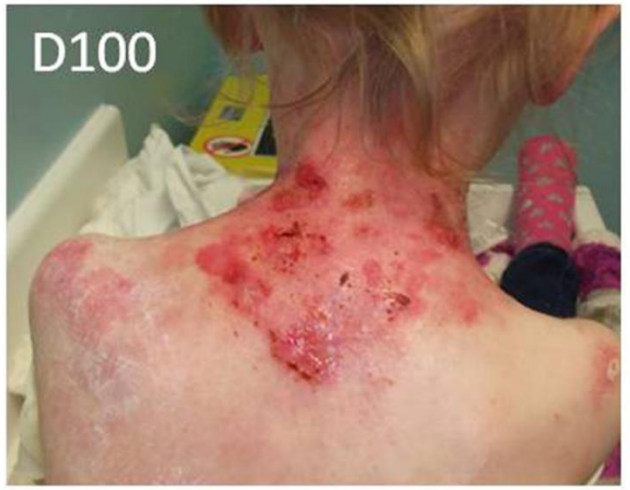
Exosomes from Mesenchymal Stromal Cells

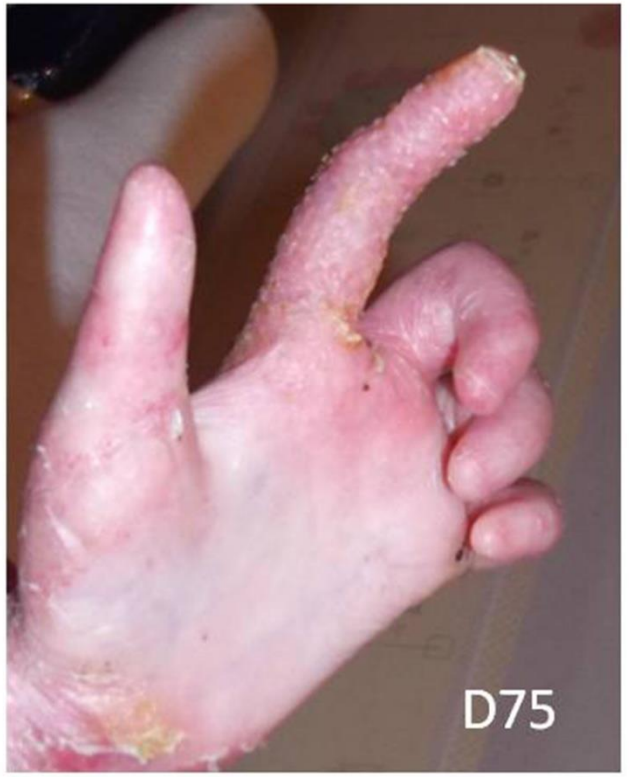
Exosomes inhibit microRNA-181a in wounds and scar tissue

Chen *et al.*
Arch Biochem Biophys 2023

Subject G







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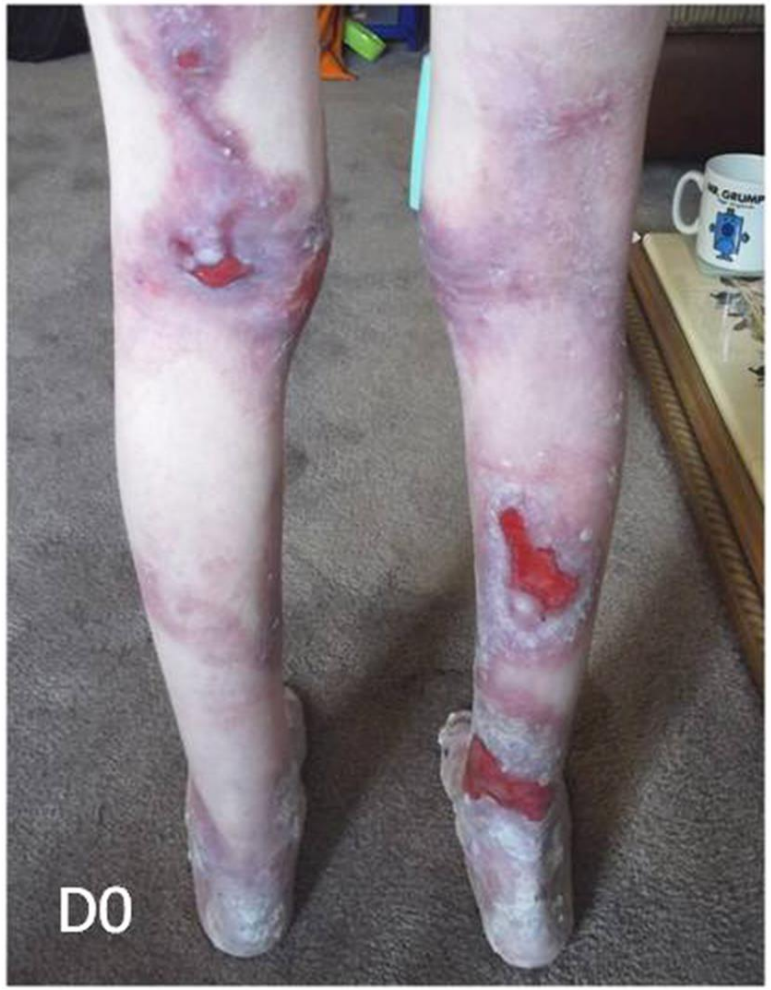
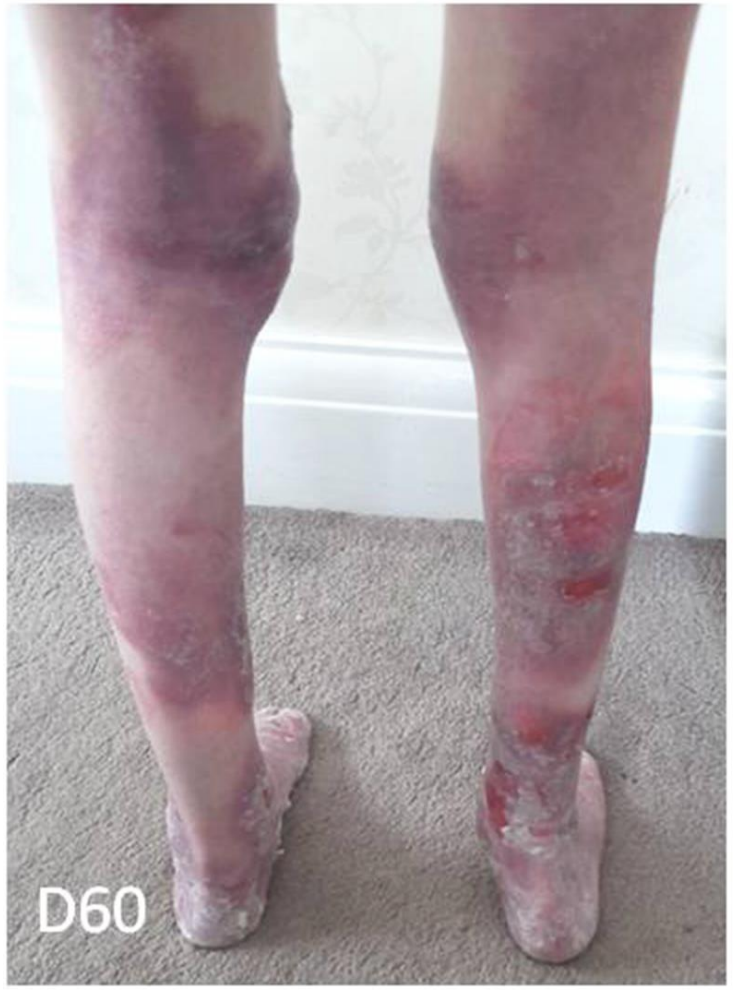
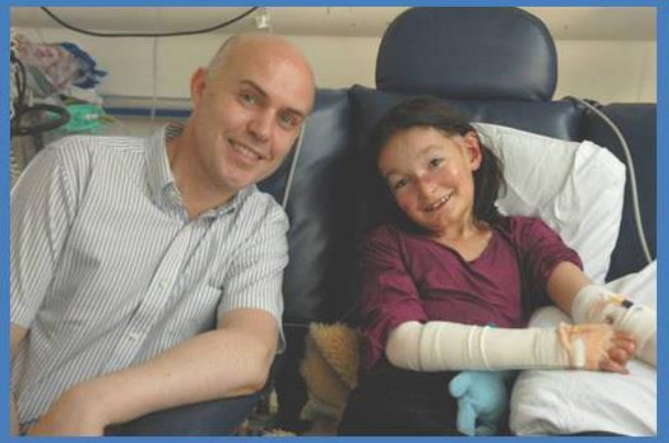








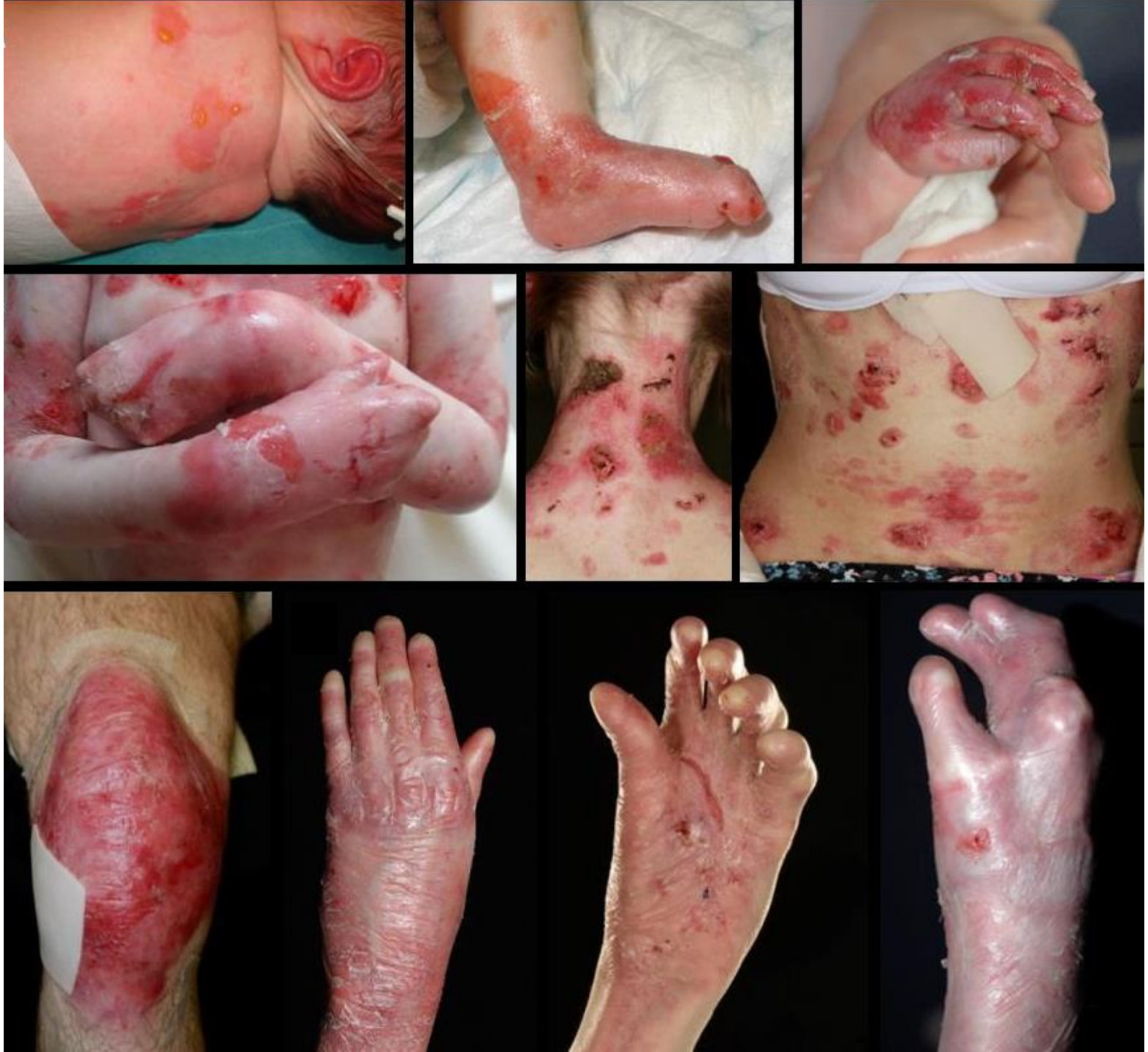


Challenges in identifying and quantifying the impact of MSCs

The importance of recording qualitative data

Optimal integration into clinical care?

Scarring/Fibrosis in DEB

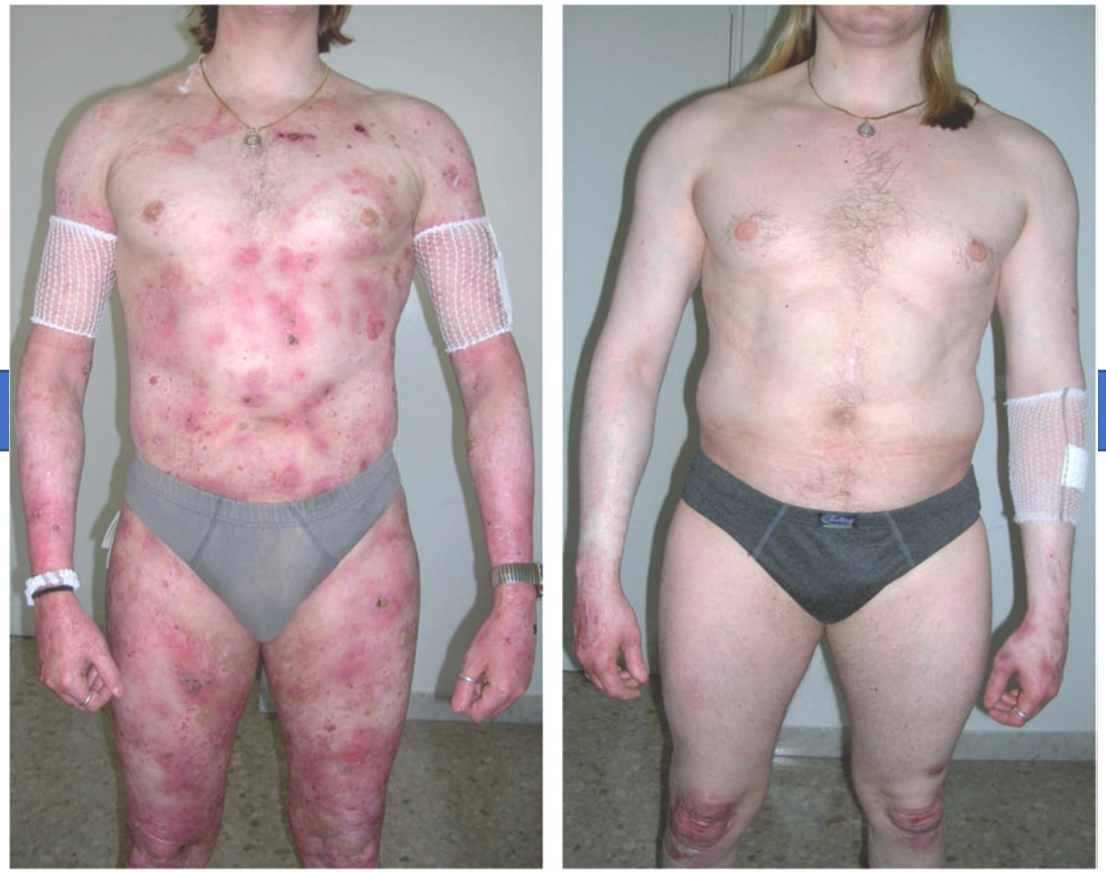


Lessons about inflammation from phenotypically discordant twins with RDEB

Enhanced TGFβ signalling

Interleukin-6 ↑

Monocyte Chemoattractant Protein-1 ↑



Interleukin-7 ↑

Decorin ↑

Inhibits TGFβ activity

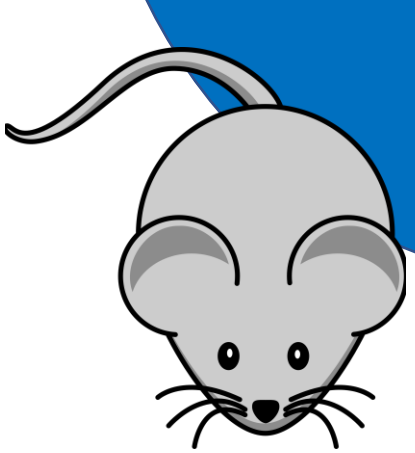
Odorisio *et al. Hum Mol Genet* 2014

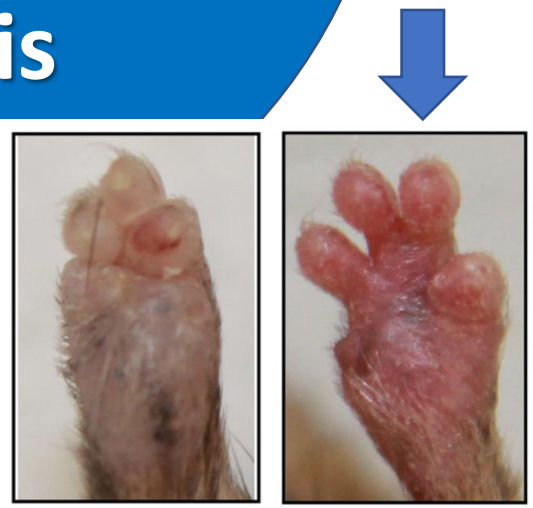
Overexpressing

Decorin

reduces RDEB

fibrosis





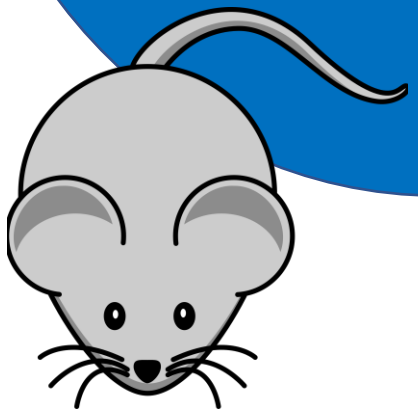
Cianfarani et al. *Matrix Biol* 2019

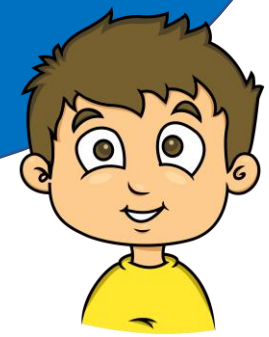
Clinical trial of

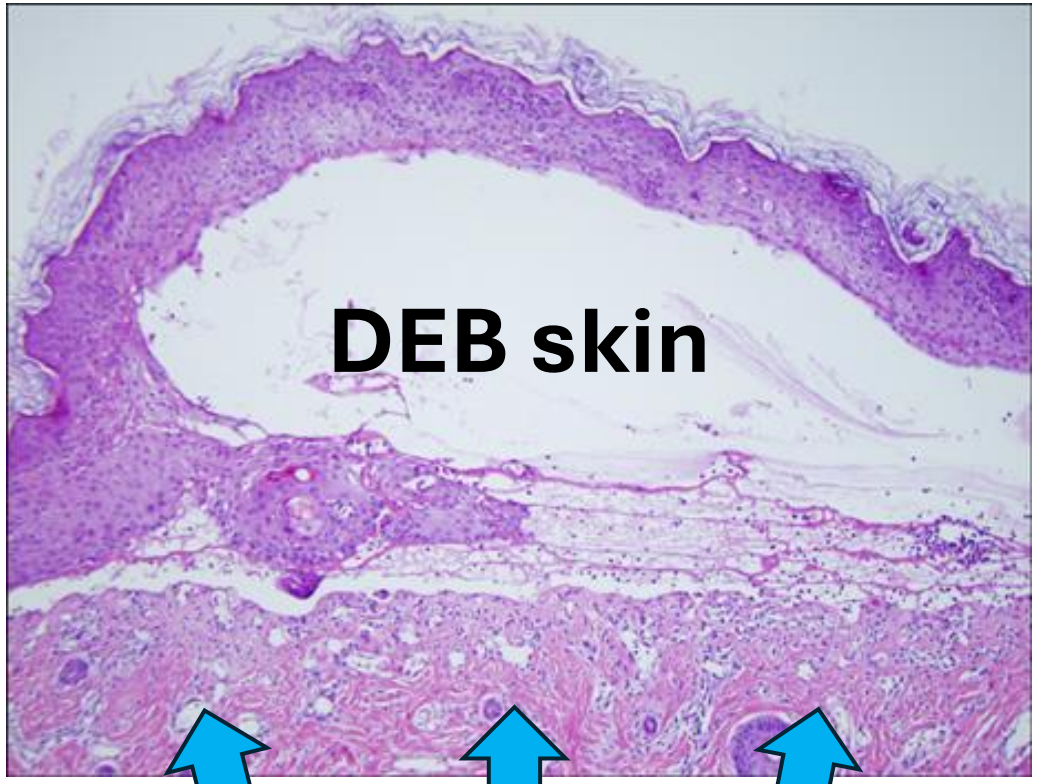
Losartan to

reduce RDEB

fibrosis







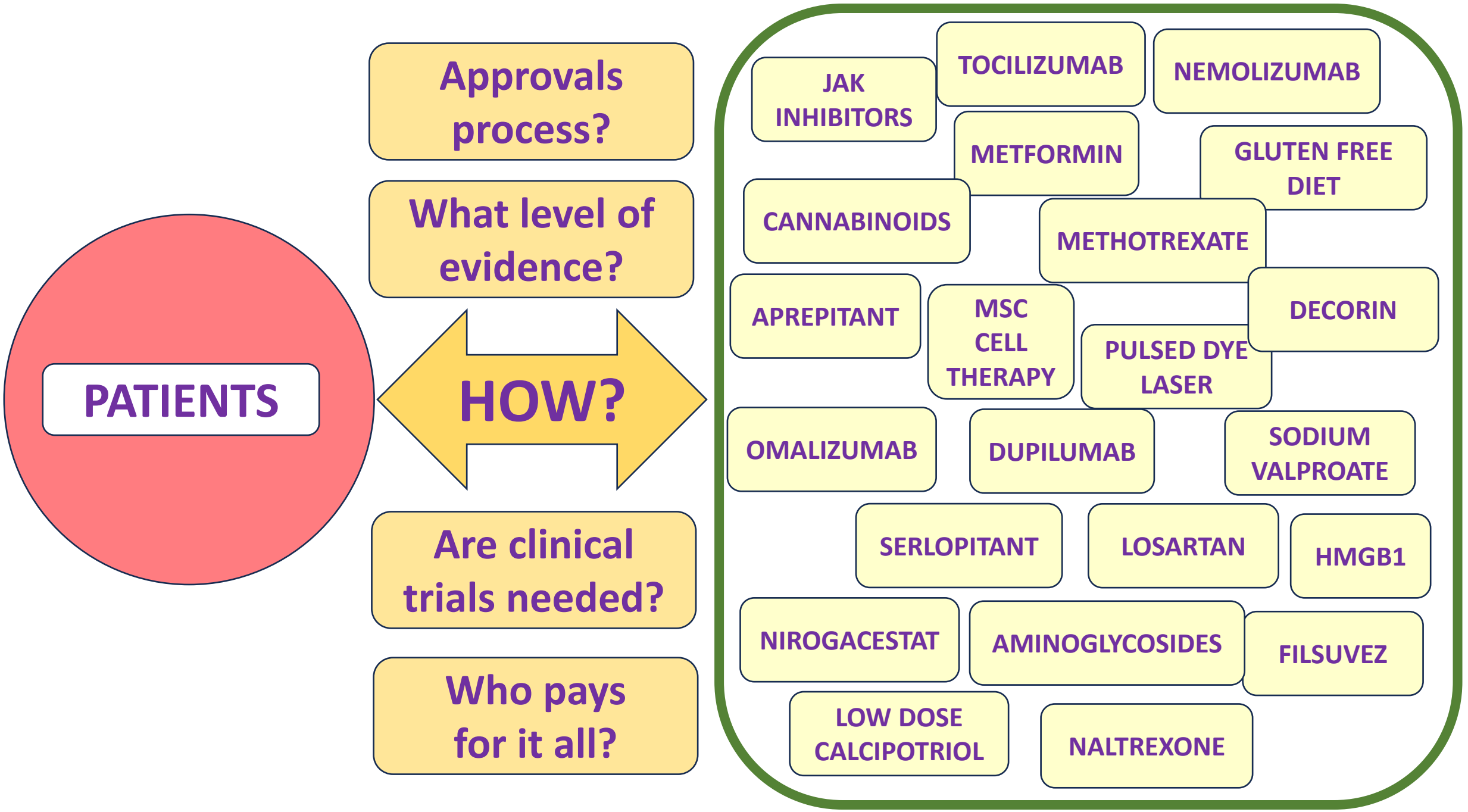
PROGRESSIVE FIBROSIS

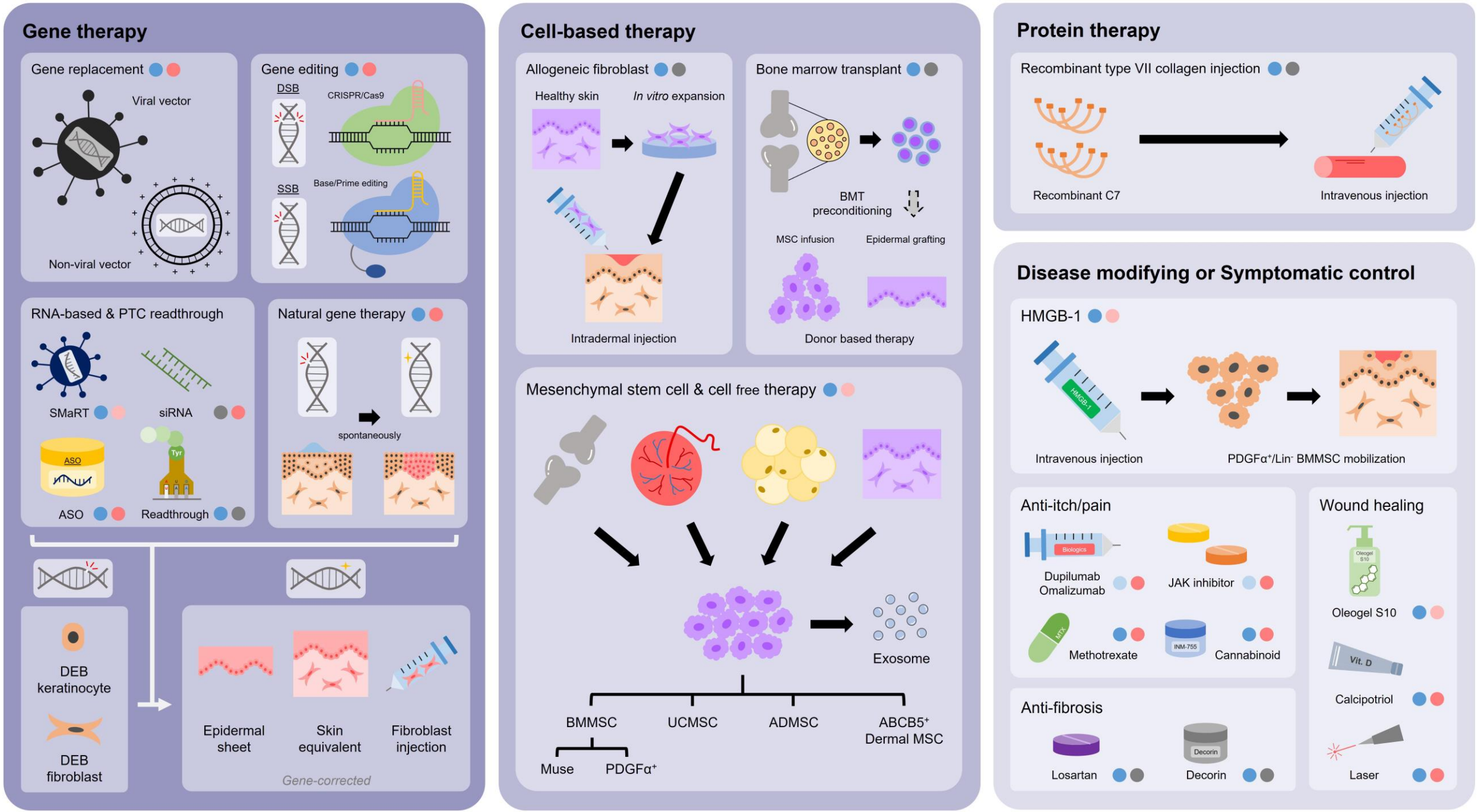
DYSREGULATED HISTONE ACETYLATION

HDACi
e.g. Valproic acid

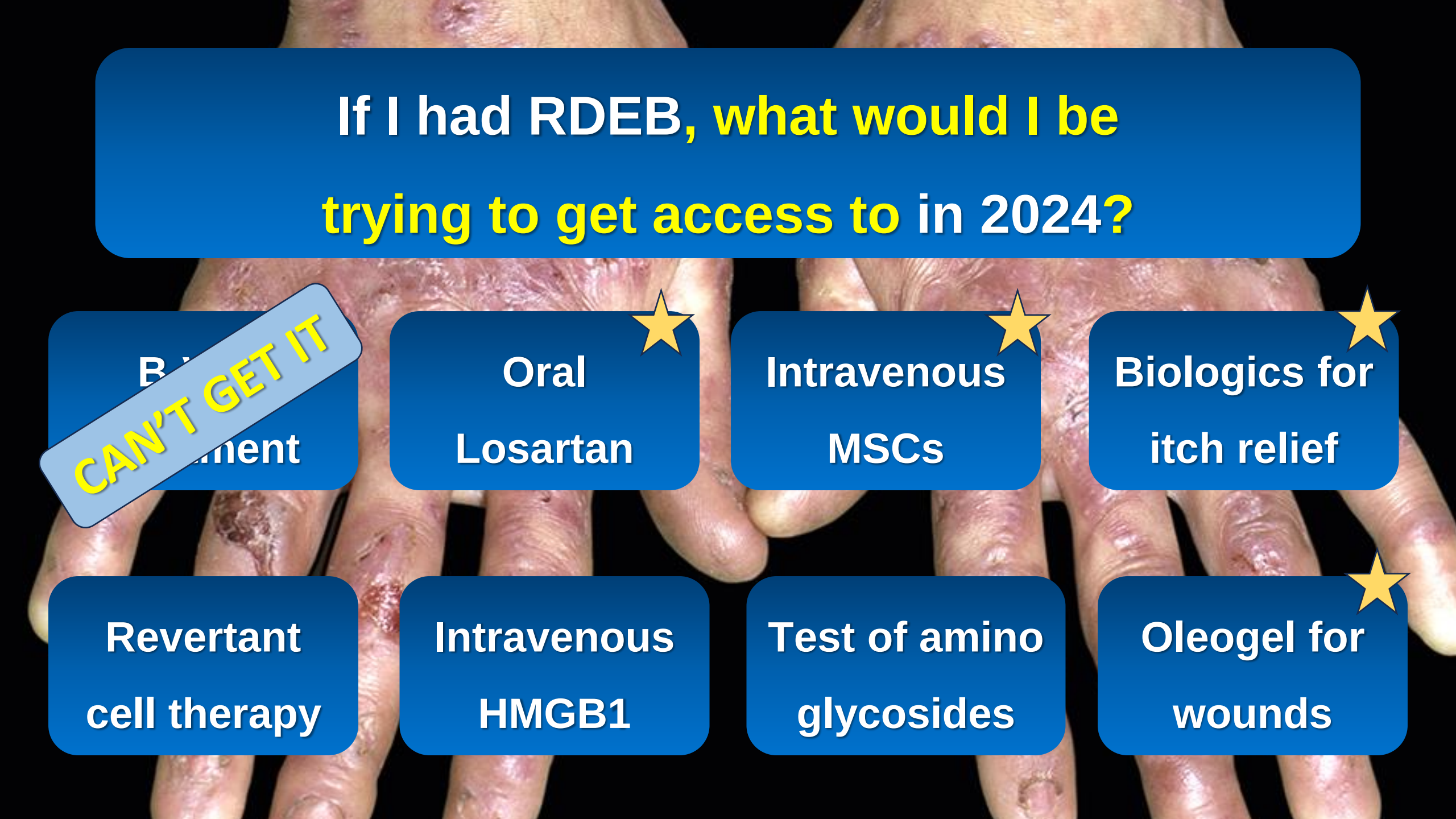
INHIBITS FIBROSIS

Primerano *et al.*
Br J Dermatol 2024


PATIENTS
HOW?
Approvals process?
What level of evidence?
Are clinical trials needed?
Who pays for it all?
JAK INHIBITORS
TOCILIZUMAB
NEMOLIZUMAB
METFORMIN
GLUTEN FREE DIET
CANNABINOIDS
METHOTREXATE
APREPITANT
MSC CELL THERAPY
DECORIN
PULSED DYE LASER
OMALIZUMAB
DUPILUMAB
SODIUM VALPROATE
SERLOPITANT
LOSARTAN
HMGB1
NIROGACESTAT
AMINOGLYCOSIDES
FILSUVEZ
LOW DOSE CALCIPOTRIOL
NALTREXONE



Hou *et al.* Ther Clin Risk Manag 2023


If I had RDEB, what would I be trying to get access to in 2024?
CAN'T GET IT
Oral Losartan
Intravenous MSCs
Biologics for itch relief
Revertant cell therapy
Intravenous HMGB1
Test of amino glycosides
Oleogel for wounds

Jouni Uitto
(1943-2022)

… I am enthusiastic that we

are approaching breakthroughs

toward phenotypic alleviation

and possibly eventual cure…..

Thank you

john.mcgrath@kcl.ac.uk

Guy's Hospital