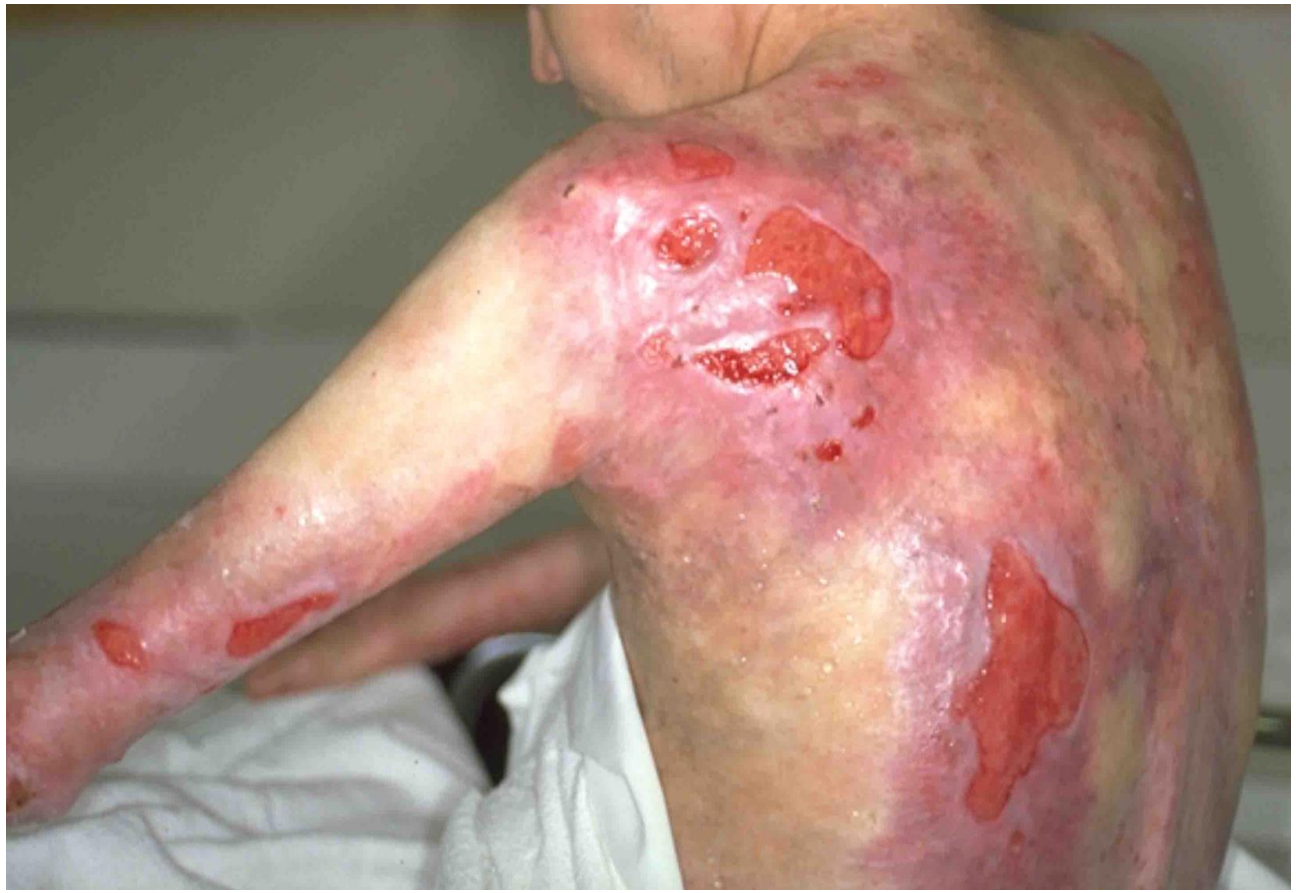
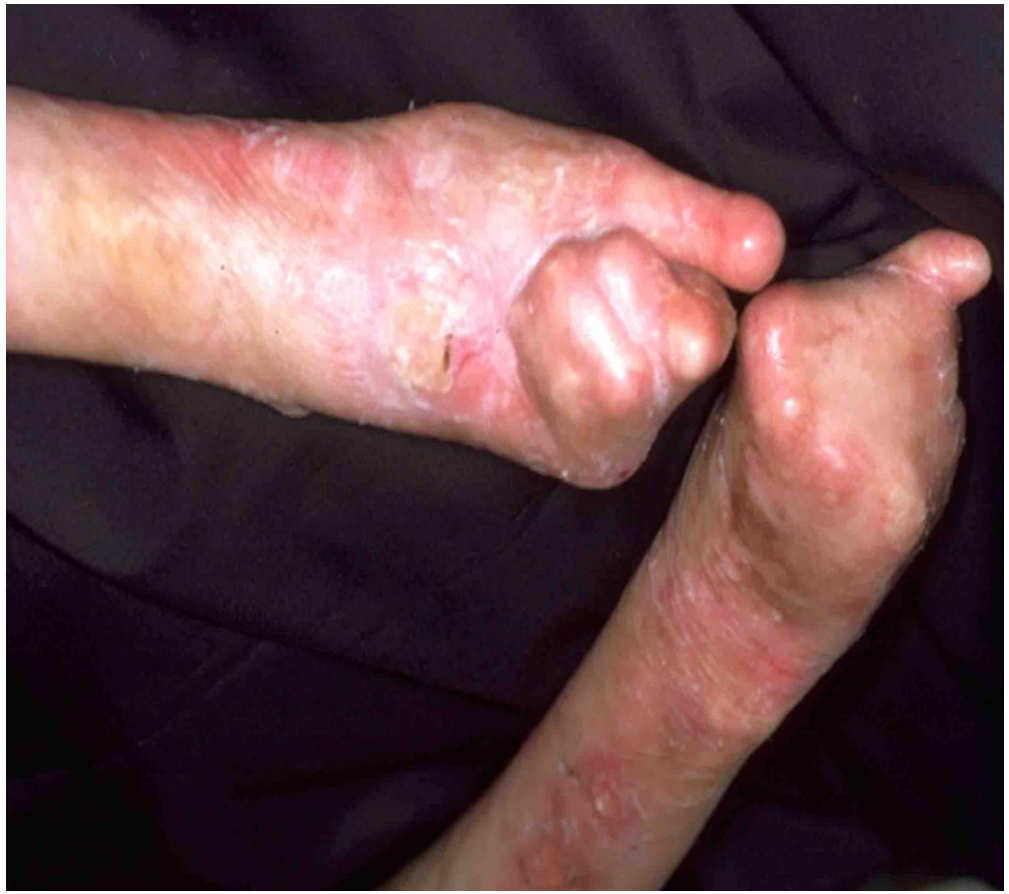
Gene therapy for epidermolysis bullosa

Peter Marinkovich
Stanford University

Recessive Dystrophic Epidermolysis Bullosa: Clinical Features

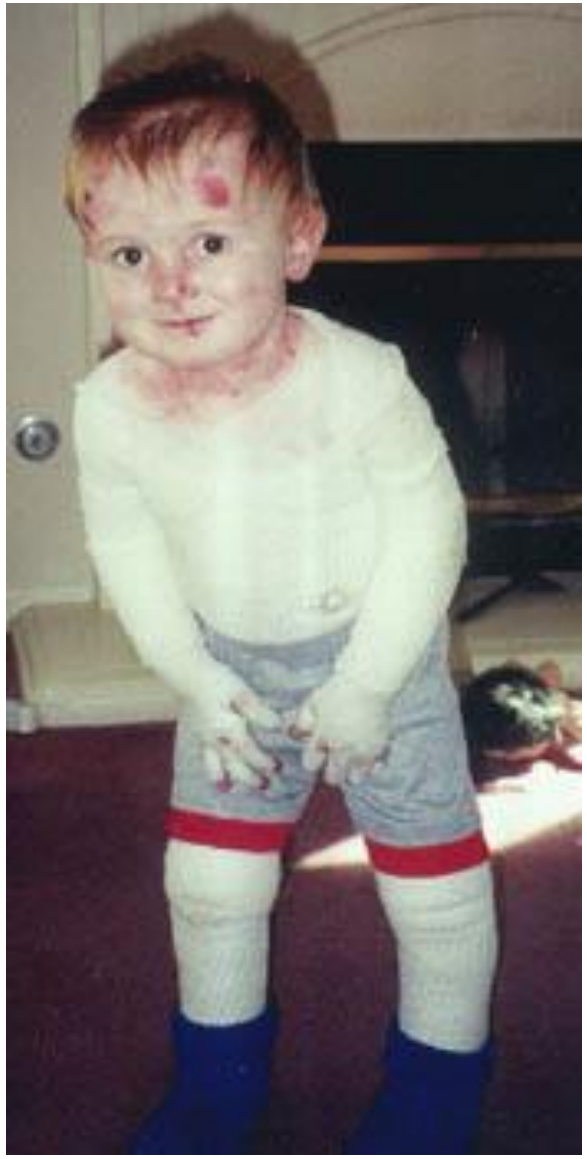


Widespread erosions and scarring



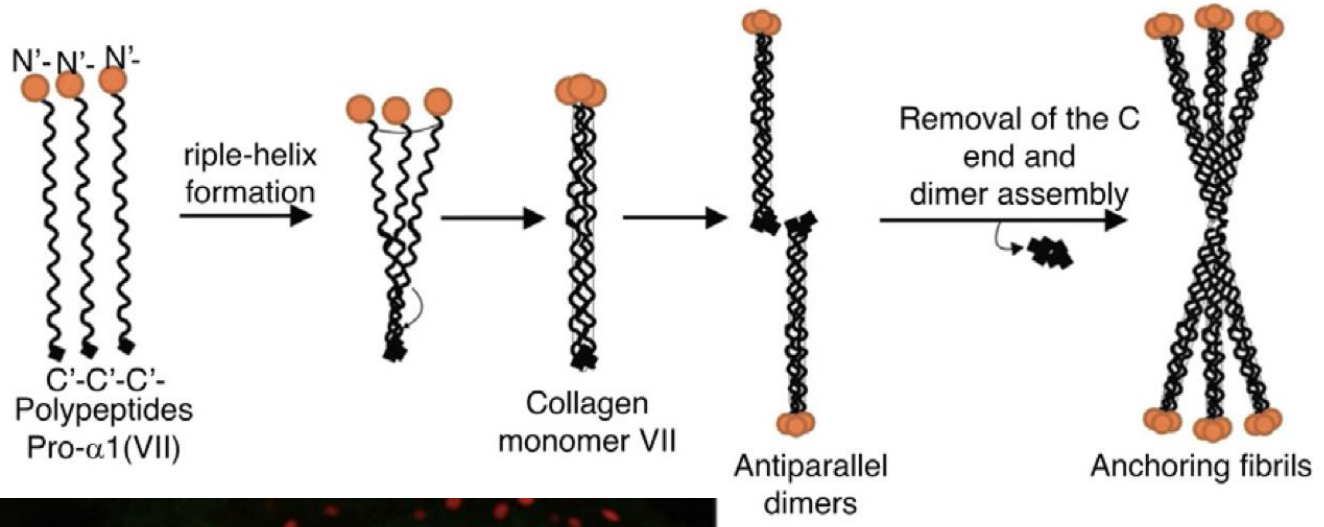
Mitten hand scarring of hands

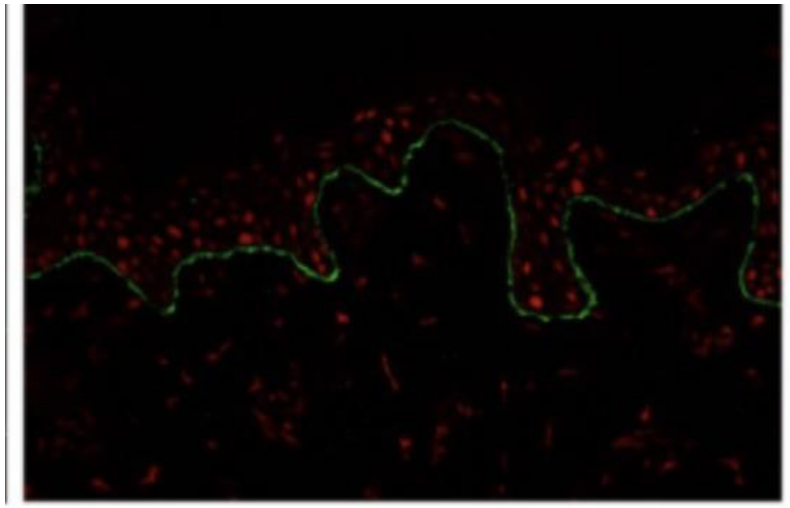
Current treatment of RDEB is only supportive



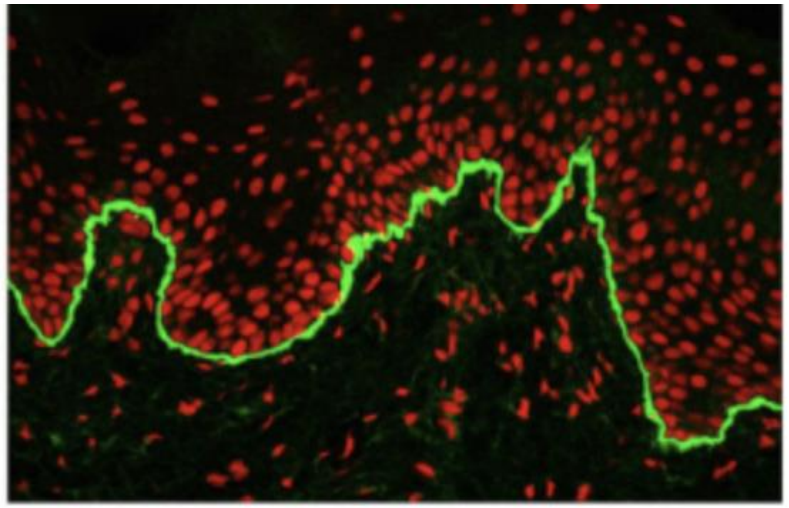
- **Wound care**
  - nonstick dressings
  - generous ointments
  - no tape!
- **Infection**
  - look for and treat!
- **Nutrition**
  - optimize!
- **Anemia**
- **Squamous cell carcinoma**

- Collagen VII, the anchoring fibril protein, is deficient in the skin of dystrophic EB patients

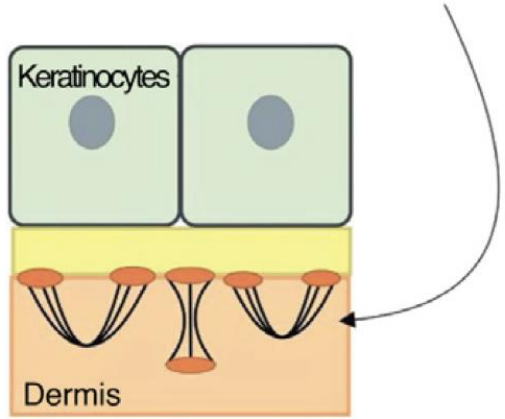




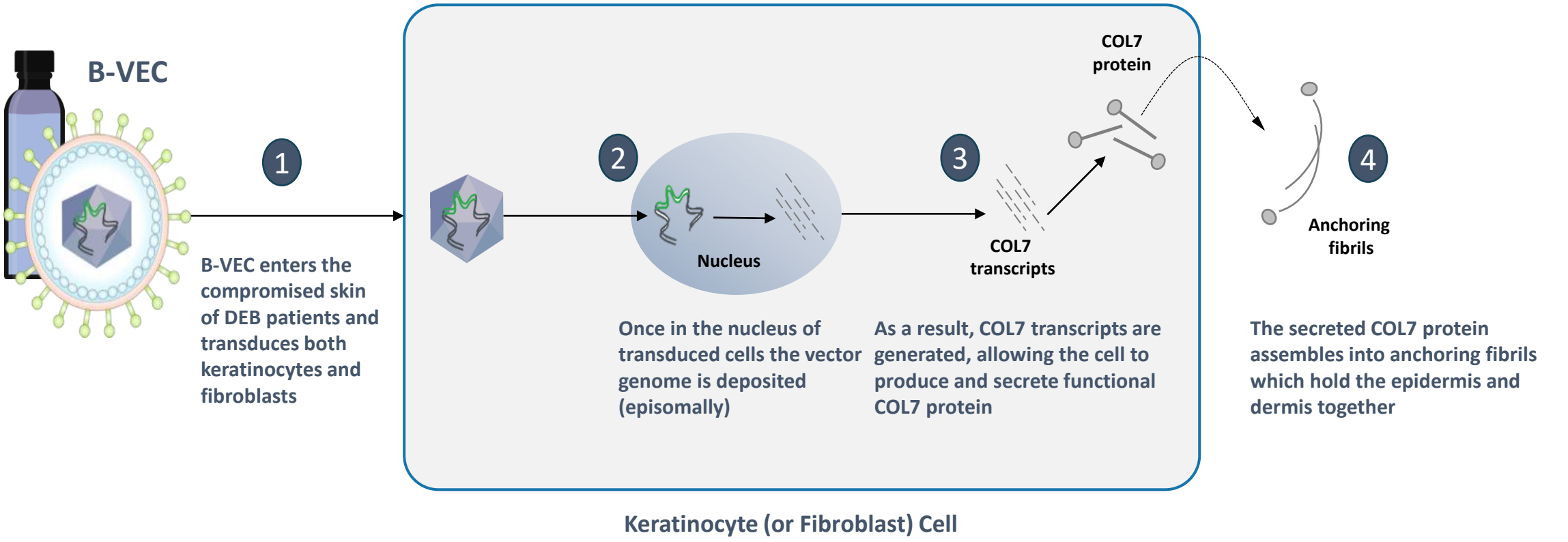
DEB skin



normal skin



Beremagene Geperpavec (B-VEC) – A novel HSV-1 based topical in vivo gene therapy that restores functional collagen VII via COL7A1 gene delivery



ARTICLES
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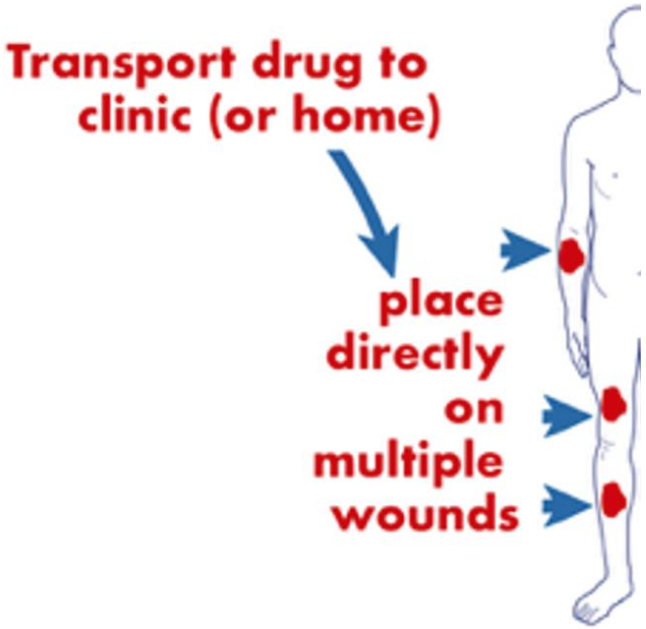
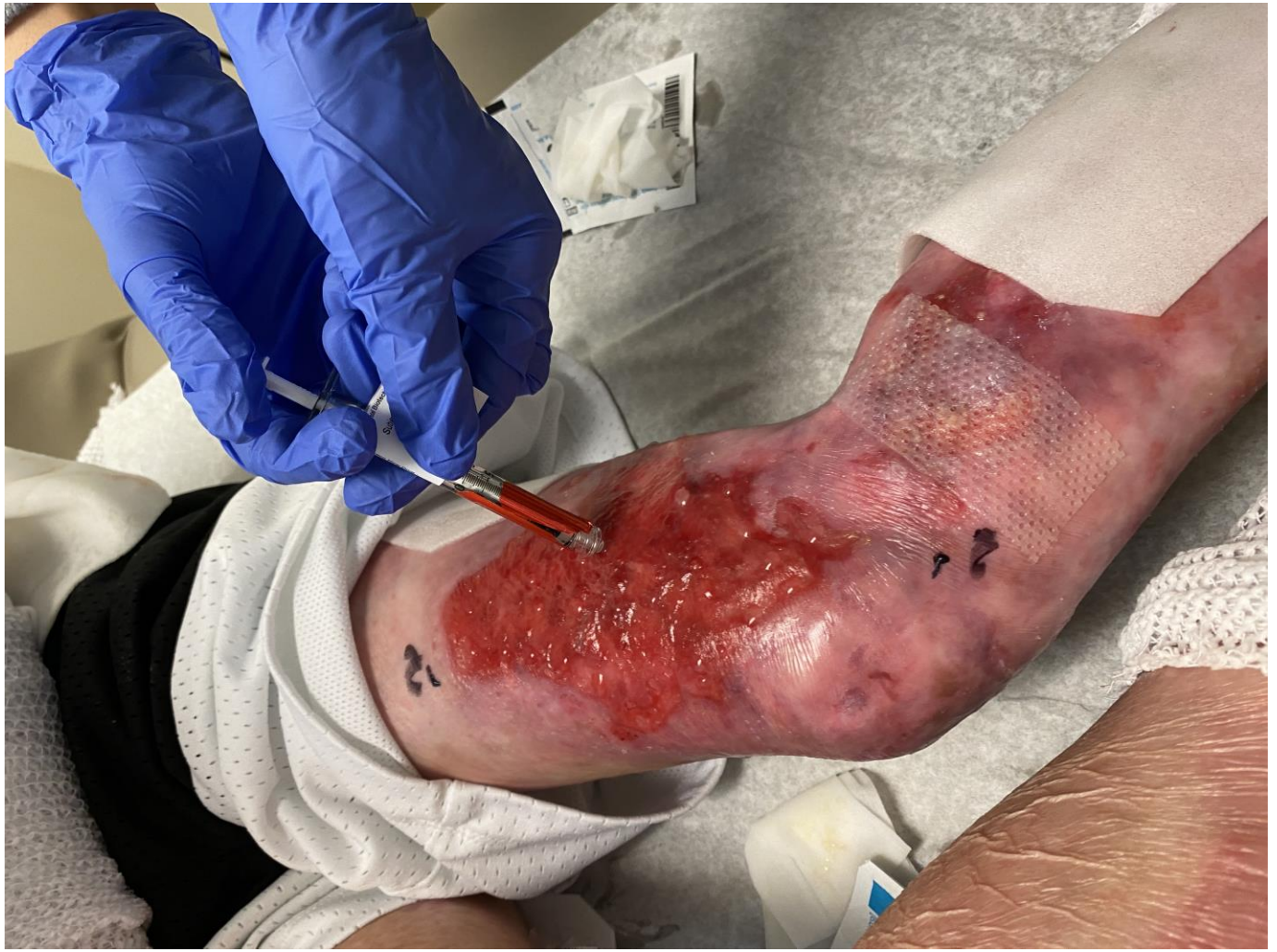
nature medicine

OPEN

In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial

Irina Gurevich[1], Pooja Agarwal[2], PeiPei Zhang[2], John A. Dolorito[1], Stacie Oliver[2], Henry Liu[2], Nicholas Reitze[2], Nikhil Sarma[2], Isin Sinem Bagci[1], Kunju Sridhar[1], Visesha Kakarla[1], Vamsi K. Yenamandra[1], Mark O'Malley[2], Marco Prisco[3], Sara F. Tufa[4], Douglas R. Keene[4], Andrew P. South[3], Suma M. Krishnan[2] and M. Peter Marinkovich[1,5]✉



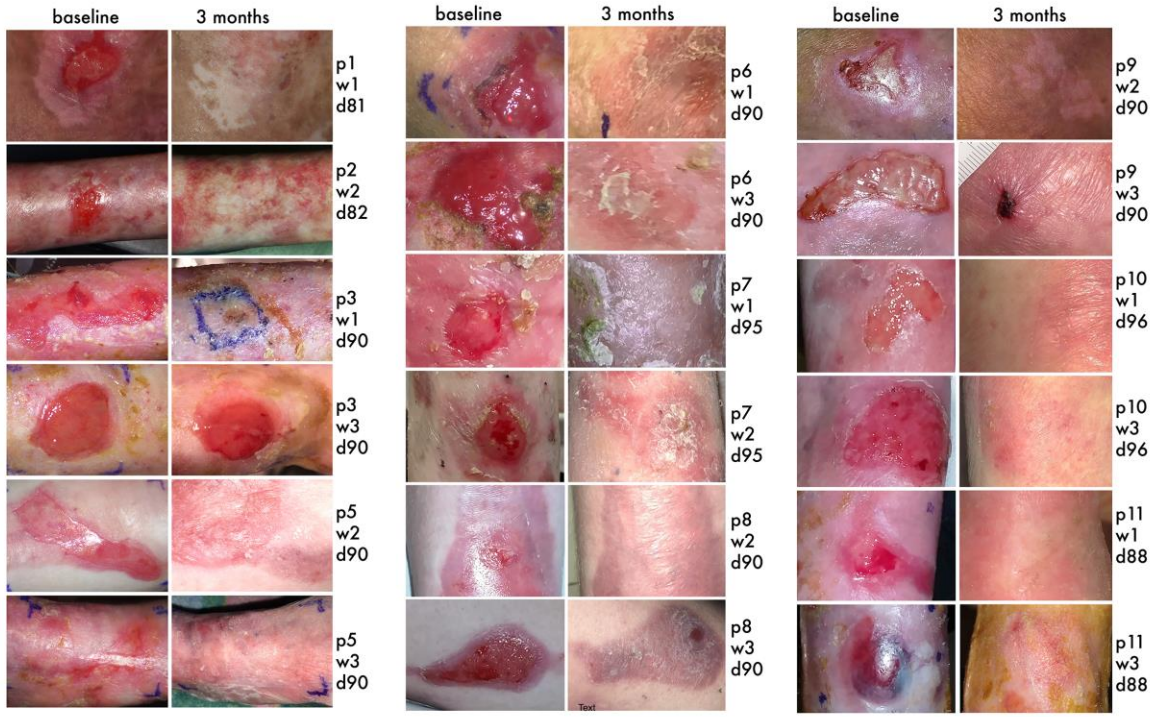


Nat Med. 2022; 28: 780-788

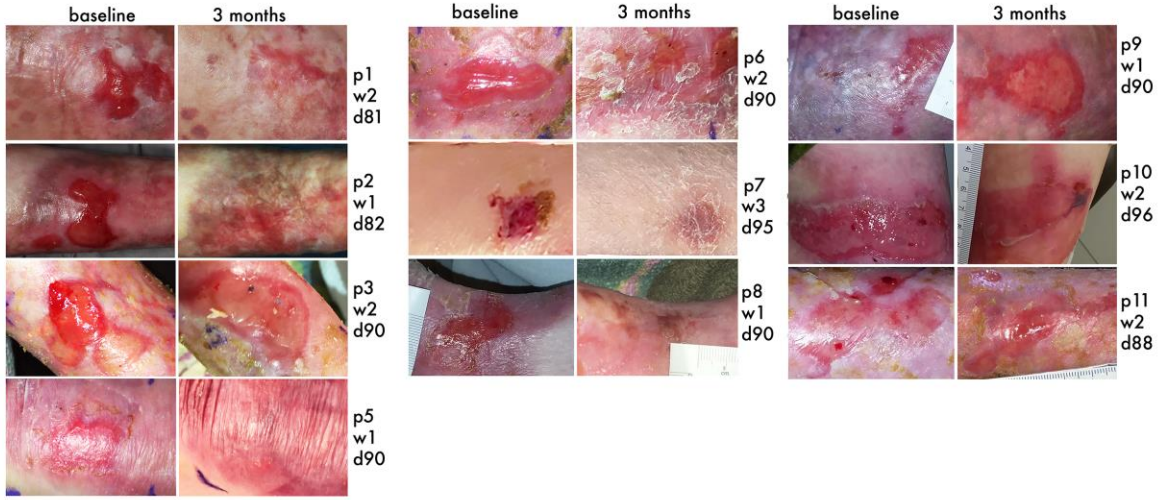
Efficient, durable healing of B-VEC treated wounds compared to matched placebo

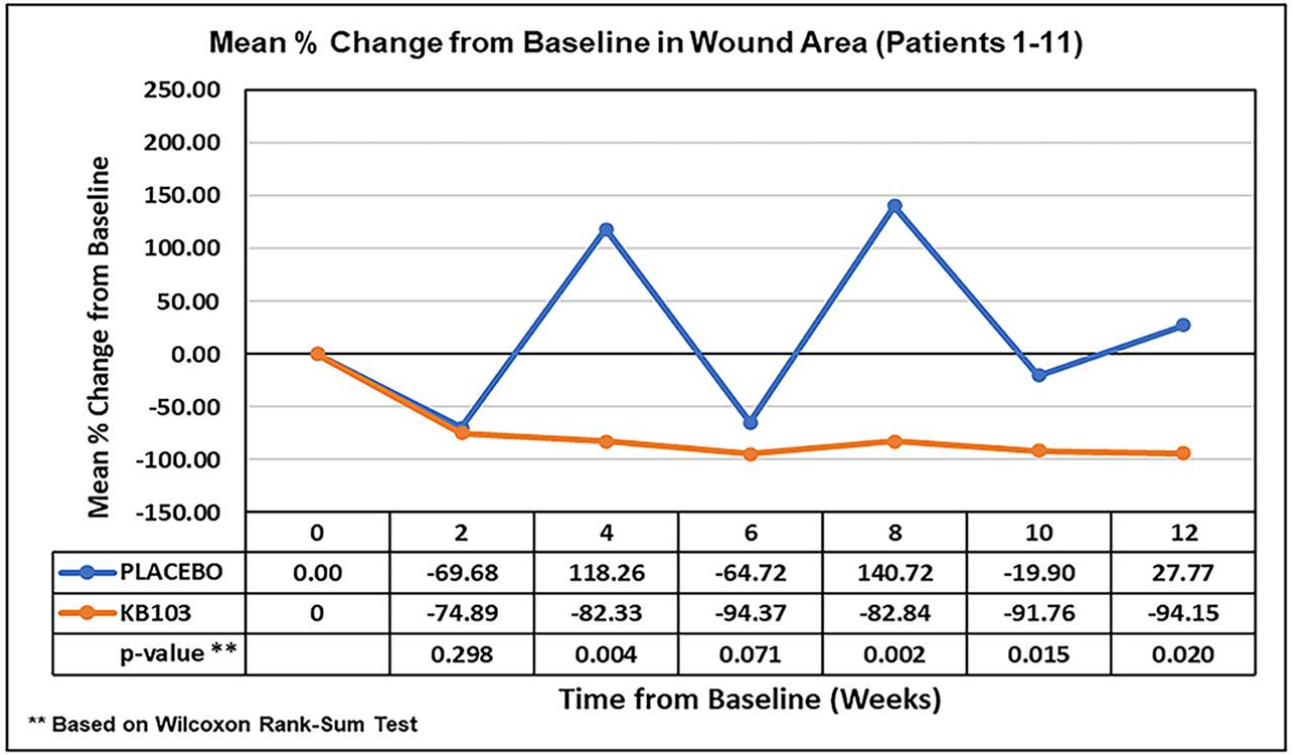
Figure 1

A. B-VEC treated wounds



B. Placebo treated wounds





	0	2	4	6	8	10	12
PLACEBO	0.00	-69.68	118.26	-64.72	140.72	-19.90	27.77
KB103	0	-74.89	-82.33	-94.37	-82.84	-91.76	-94.15
p-value **		0.298	0.004	0.071	0.002	0.015	0.020

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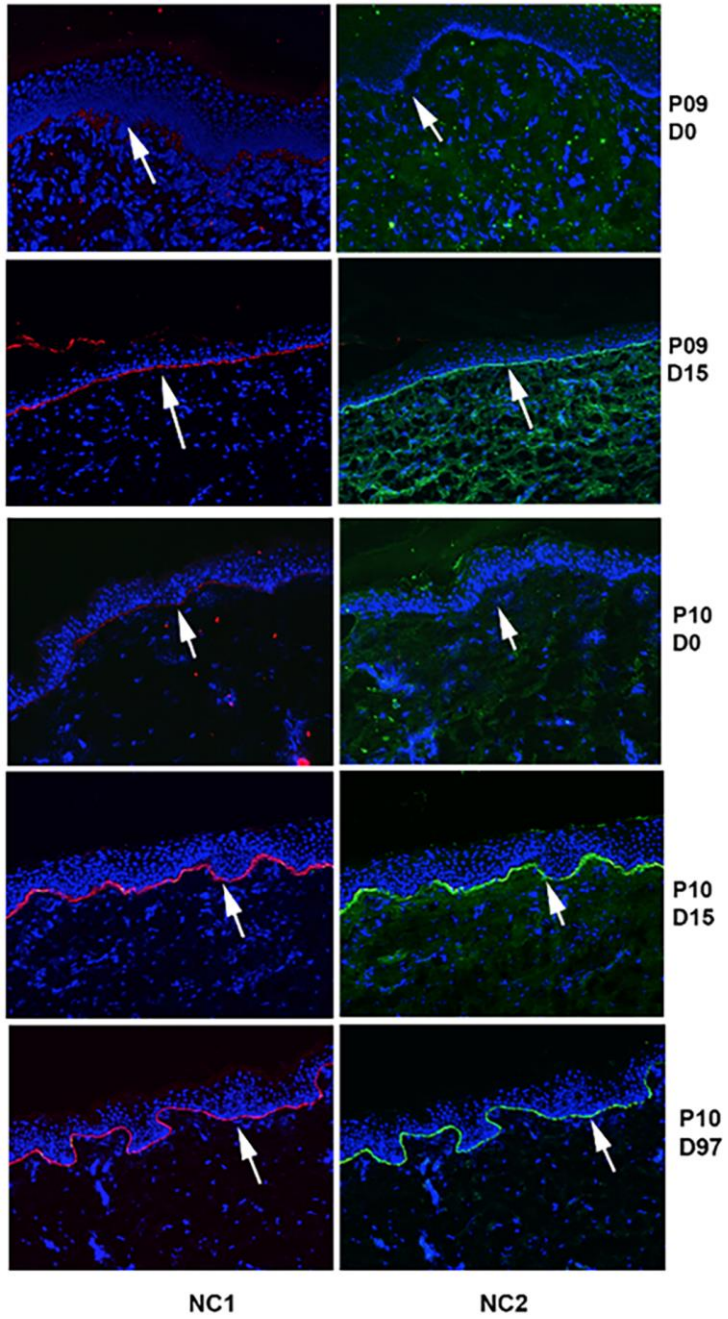
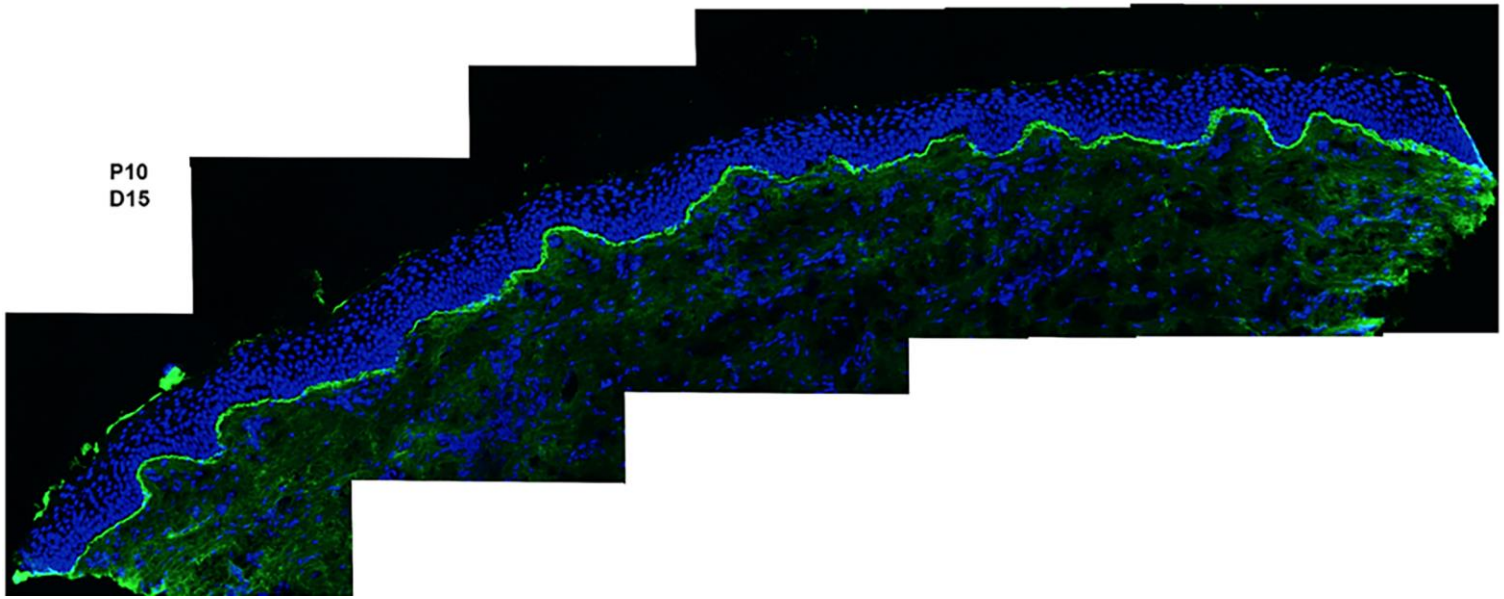
Collagen VII expression in patient skin following topical B-VEC applications





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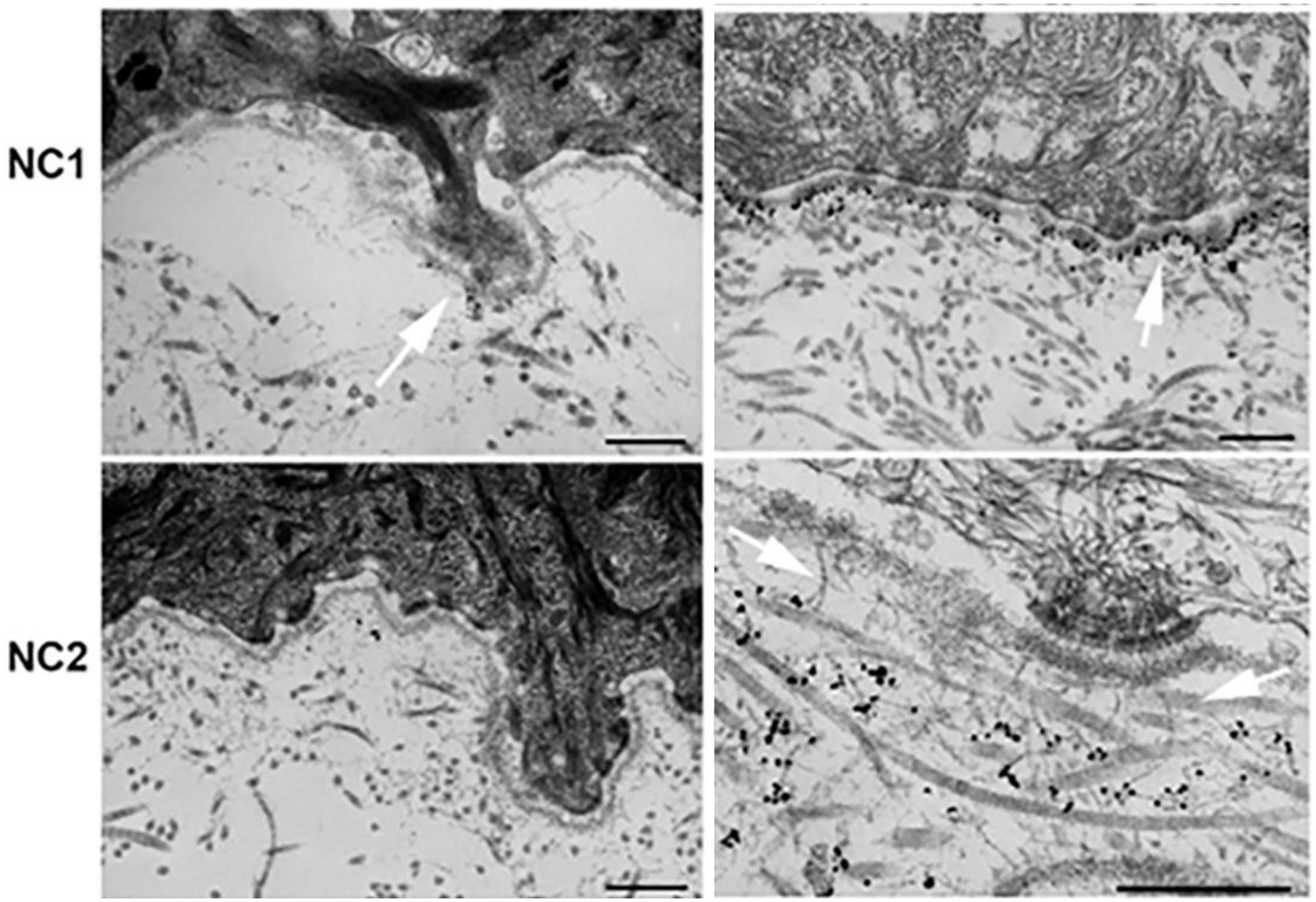
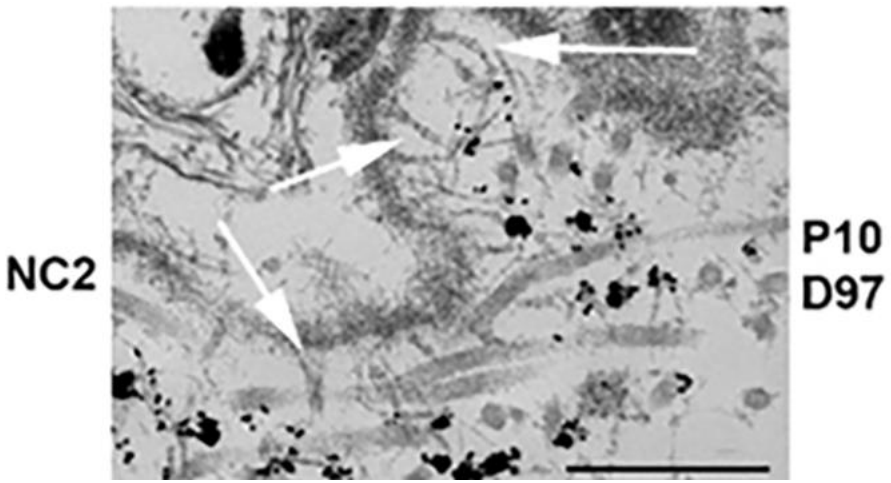
Collagen VII and anchoring fibrils in patient skin following topical B-VEC





Baseline

Day 97 after B-VEC therapy

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The NEW ENGLAND JOURNAL of MEDICINE

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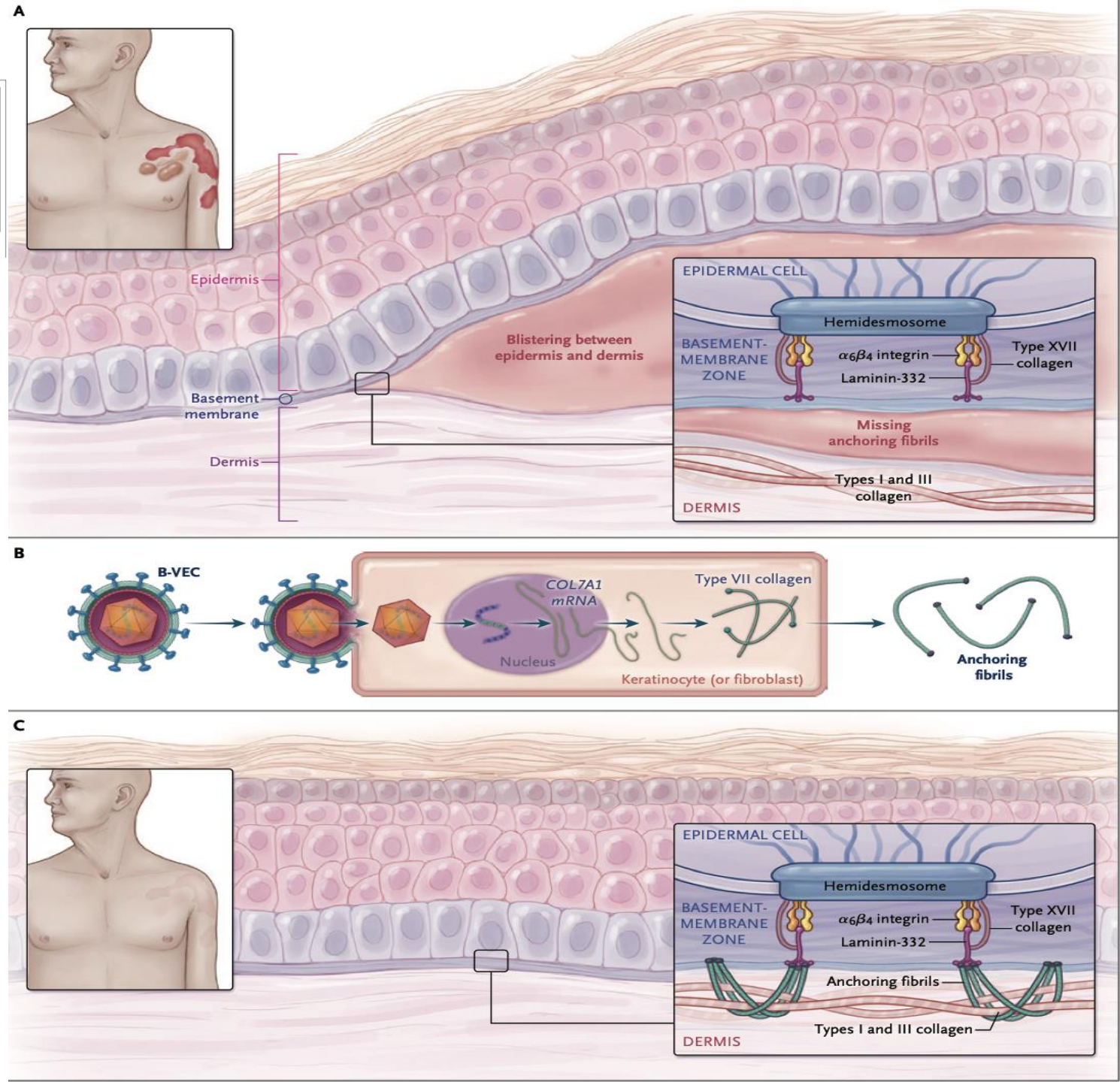
Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa

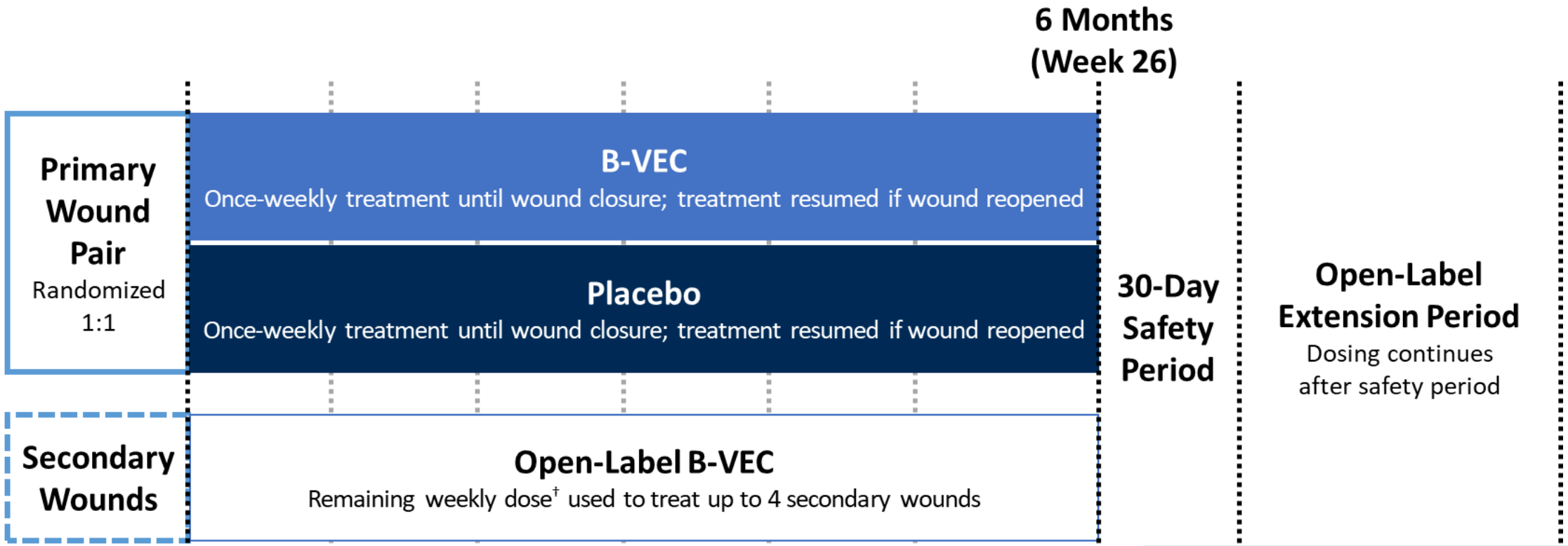
Shireen V. Guide, M.D., Mercedes E. Gonzalez, M.D., I. Sinem Bağcı, M.D., Brittani Agostini, B.S.N., Hubert Chen, M.D., Gloria Feeney, B.S., Molly Steimer, B.S., Binoy Kapadia, B.S., Kunju Sridhar, Ph.D., Lori Quesada Sanchez, B.S., Franshesca Gonzalez, B.S., Matthew Van Ligten, B.S., Trevor J. Parry, Ph.D., Surya Chitra, Ph.D., Lisa A. Kammerman, Ph.D., Suma Krishnan, M.S., and M. Peter Marinkovich, M.D.



Methods

Trial Design and Oversight – A pivotal trial to test redosable in vivo topical gene therapy

- Phase 3, double-blind, intrapatient randomized, placebo-controlled trial evaluating B-VEC efficacy and safety in DEB
- Children and adults with DEB were recruited from three US sites
- Two wounds were selected of similar size, anatomical region, and appearance (defined as the primary wound pair)
- Randomized wound pairs received weekly application of either B-VEC or placebo for 26 weeks until wound closure



Guide SV, et al. *N Engl J Med* 2022; 387: 2211-9.

Methods

End Points – primary end point of 100% wound healing at 6 months- a high bar!

Primary End Point

- Binary indicator of primary wounds with complete wound healing at 6 months
- Only wounds healed for at least two consecutive weeks were counted as having had a response
- Complete wound healing defined as 100% wound closure

Secondary End Points

- Key secondary end point: binary indicator of primary wounds with complete healing at 3 months
- Other secondary end point: change from baseline to Weeks 22, 24, and 26 in pain severity during changes in wound dressing, assessed using a VAS (for patients ≥6 years of age) and the FLACC-R scale (for patients <6 years of age)

Safety Endpoints

- Monitoring of adverse events, physical examination, vital signs, and clinical laboratory tests
- Immunologic evaluation included testing for antibodies against HSV-1 and C7

Guide SV, et al. *N Engl J Med* 2022; 387: 2211-9.

Results

Efficacy – Primary End Point and Key Secondary End Point

	Primary Wounds Exposed to B-VEC, n (%) (N=31)	Primary Wounds Exposed to Placebo, n (%) (N=31)	Absolute Difference, percentage points (95% CI)	P Value
Primary end point: complete wound healing at 6 months*	20.9 (67)	6.7 (22)	46 (24 , 68)	0.002
Key secondary end point: complete wound healing at 3 months†	21.9 (71)	6.1 (20)	51 (29, 73)	<0.001

Guide SV, et al. *N Engl J Med* 2022; 387: 2211-9.

Results

Safety

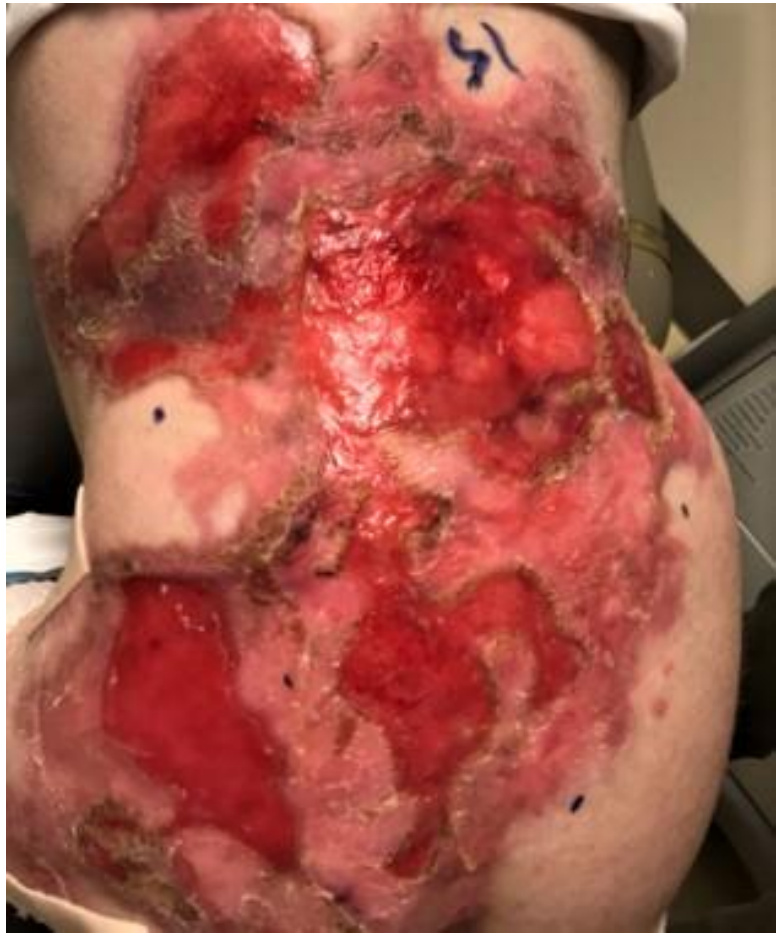
- Majority of adverse events were mild or moderate in severity, as assessed by the investigators
- Five serious adverse events occurred in three patients:
  - One patient was hospitalized three times, once for diarrhea and twice for severe anemia
  - One patient was hospitalized for treatment of cellulitis
  - One patient was hospitalized for a positive blood culture related to a hemodialysis catheter
  - None were considered to be related to B-VEC or placebo
- One adverse event, mild erythema, was considered to be related to B-VEC
- No adverse events led to discontinuation of B-VEC or placebo
- The most common adverse events were pruritus, chills, and squamous cell carcinoma of the skin, each of which occurred in three patients (10%)
  - All three cases of squamous cell carcinoma occurred at wound sites that did not receive B-VEC or placebo

	Safety Population (n=31)
Total number of adverse events	45
Patients with ≥ 1 adverse event, n (%)*	18 (58)
Mild	15 (48)
Moderate	3 (10)
Severe	2 (6)
Serious‖	3 (10)
Related to B-VEC or placebo	1 (3)
Leading to discontinuation of B-VEC or placebo	0
Adverse events reported in ≥5% of patients, n (%)*,†	
Skin and subcutaneous disorders	
Pruritus	3 (10)
Erythema	2 (6)
Rash	2 (6)
General disorders and site conditions: chills	3 (10)
Neoplasms: squamous cell carcinoma of skin	3 (10)
Respiratory, thoracic, and mediastinal disorders	
Cough	2 (6)
Rhinorrhea	2 (6)

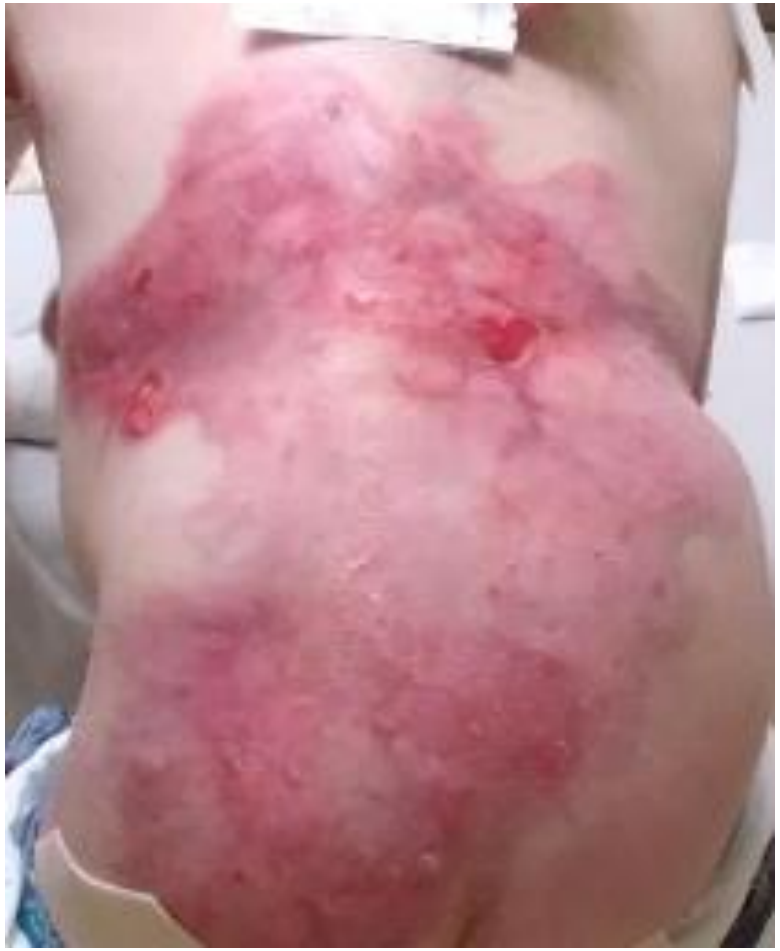
Data are for adverse events that emerged or worsened after the first application of B-VEC or placebo.
*At each level of summarization, a patient was counted once if one or more events occurred.
‖Five serious adverse events occurred in three patients: one patient was hospitalized three times, once for diarrhea (severe adverse event) and twice for severe anemia (both severe adverse events); one patient was hospitalized for treatment of cellulitis (severe adverse event); and one patient was hospitalized for a positive blood culture related to a hemodialysis catheter (moderate adverse event).
†Adverse events were classified according to system organ class and preferred term in the *Medical Dictionary for Regulatory Activities*, version 24.1.

Guide SV, et al. *N Engl J Med* 2022; 387: 2211-9.

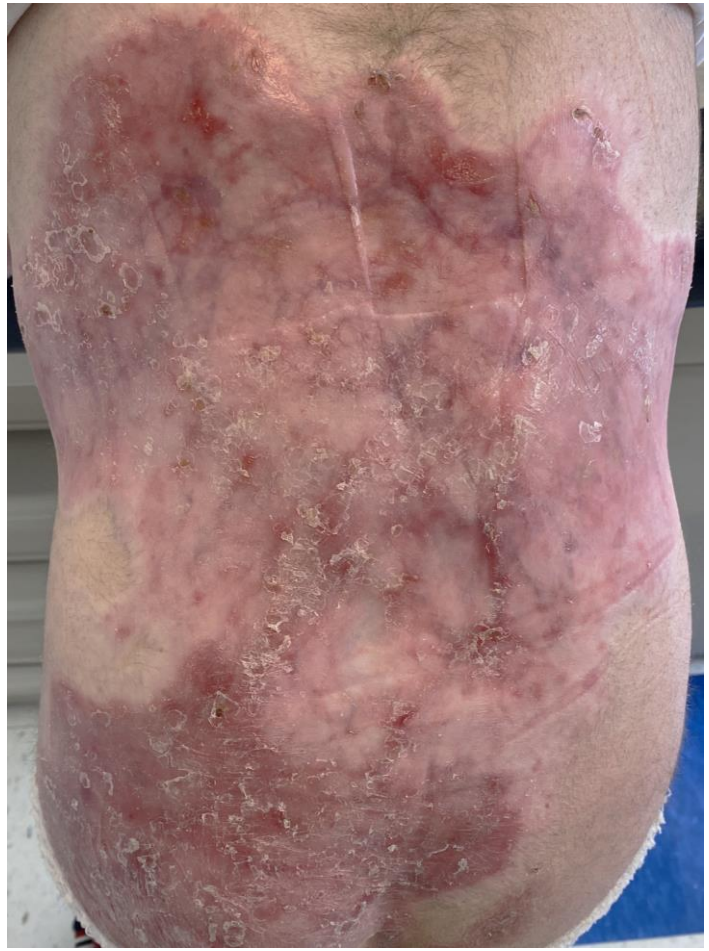
Results in the skin– long term efficacy and durability of therapy



Baseline April 2021



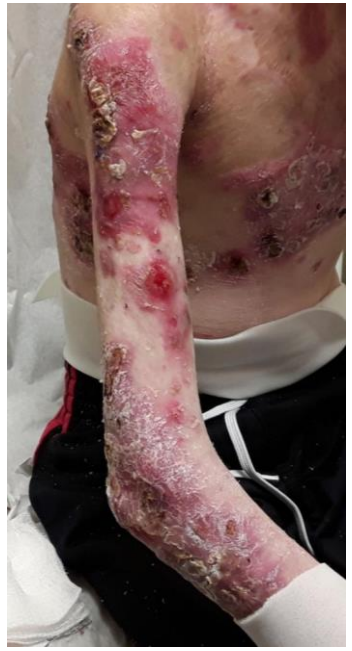
end of Phase 3 October 2021



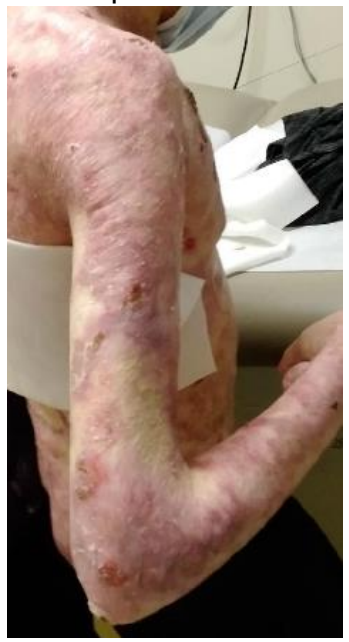
Off therapy 17 months
May 2023

Four year follow up of RDEB patient on topical BVEC

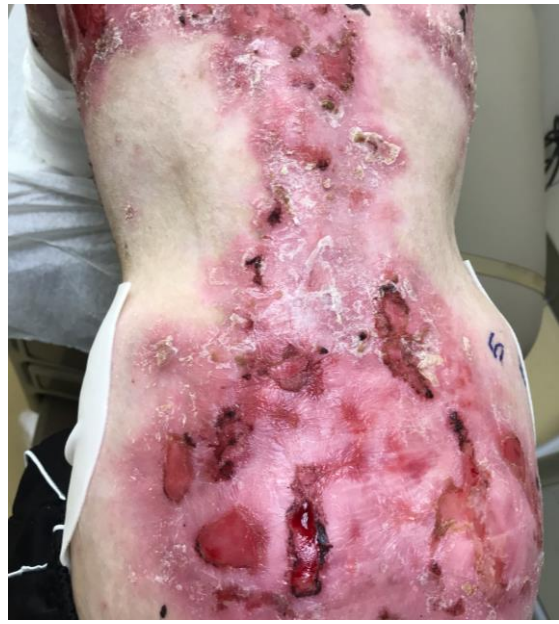
April 2019



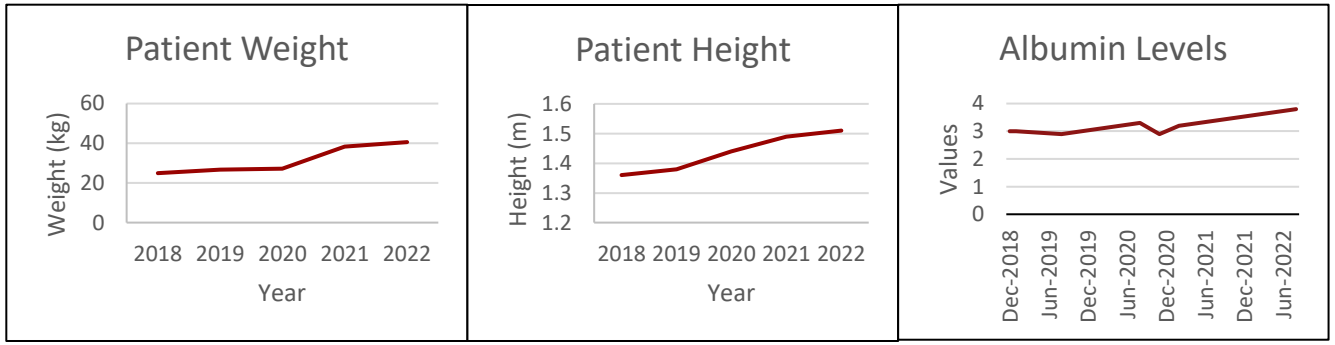
April 2023



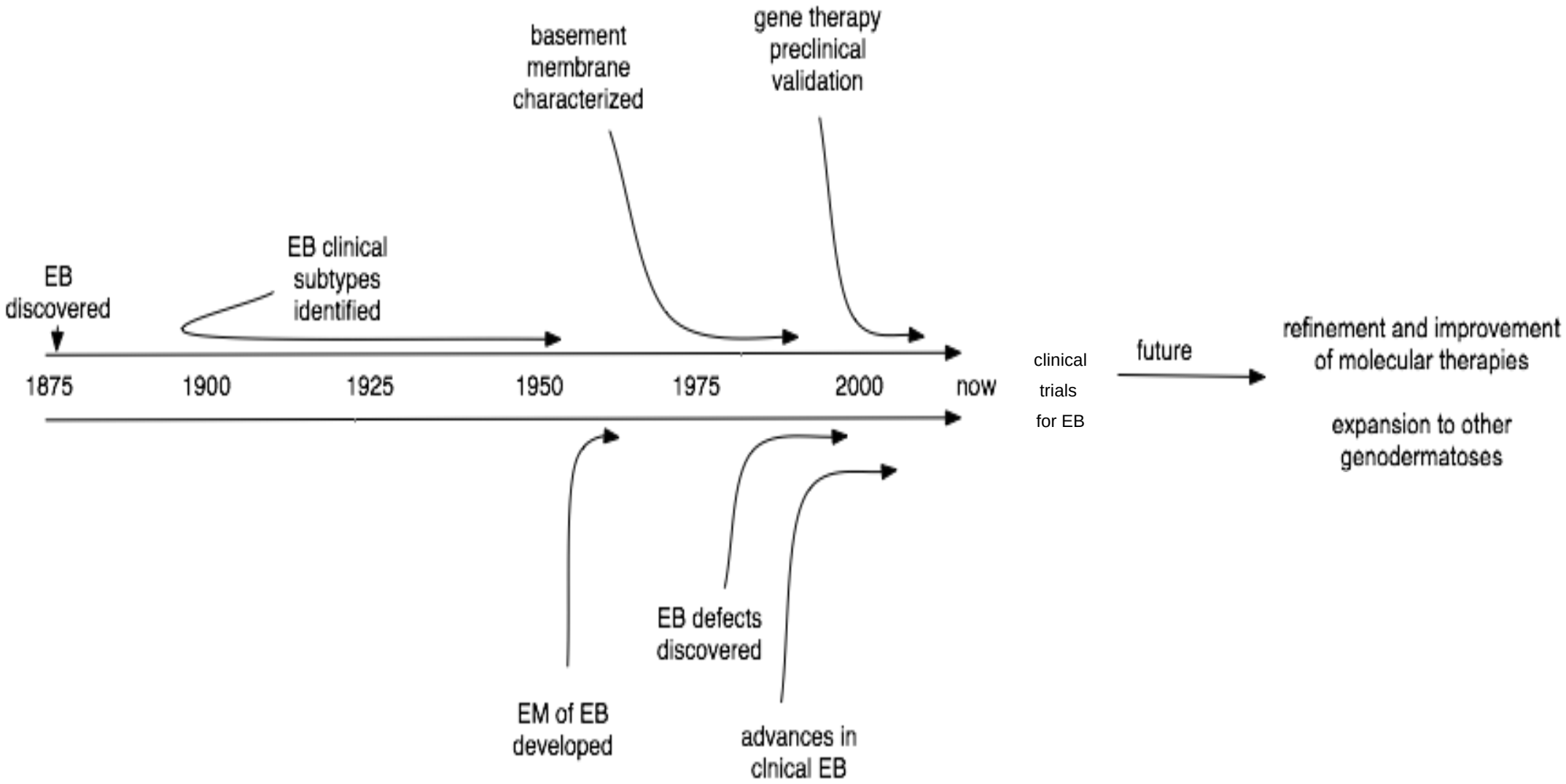
August 2020



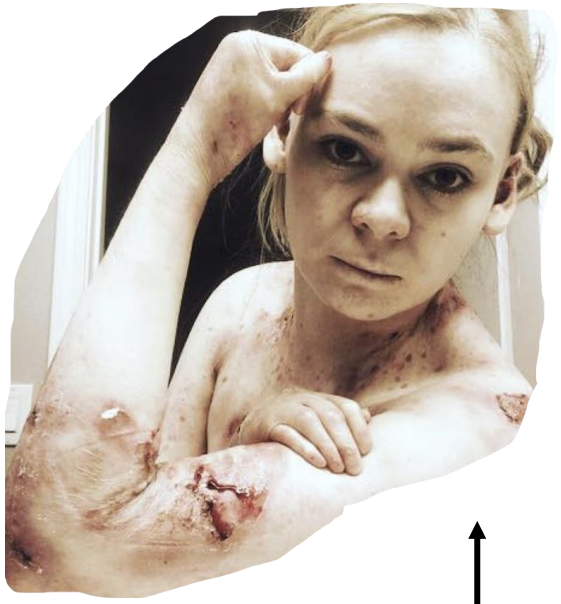
May 2023



History of Epidermolysis Bullosa

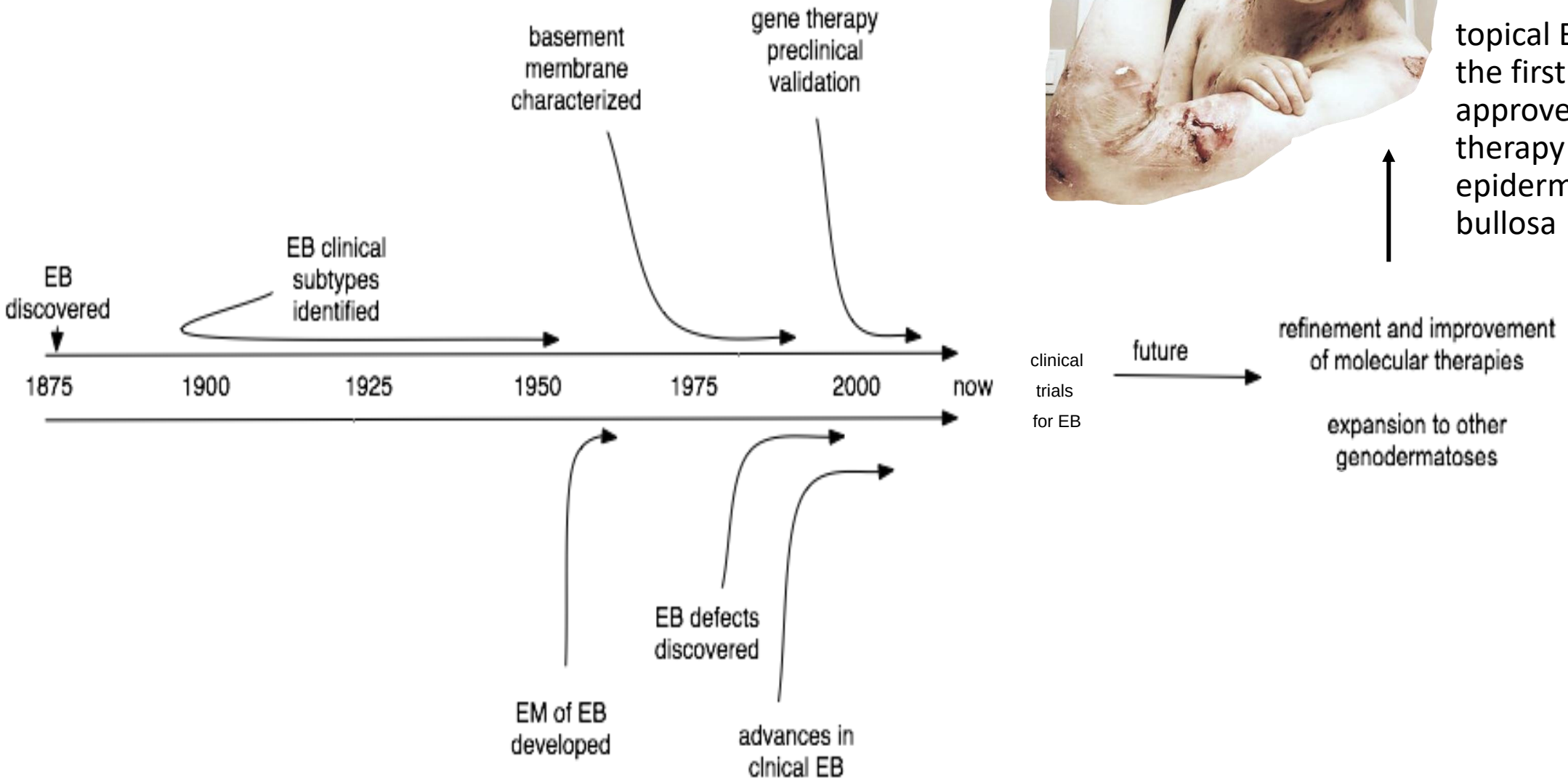


History of Epidermolysis Bullosa



May 19, 2023

topical BVEC, the first approve gene therapy for epidermolysis bullosa




One more thing…

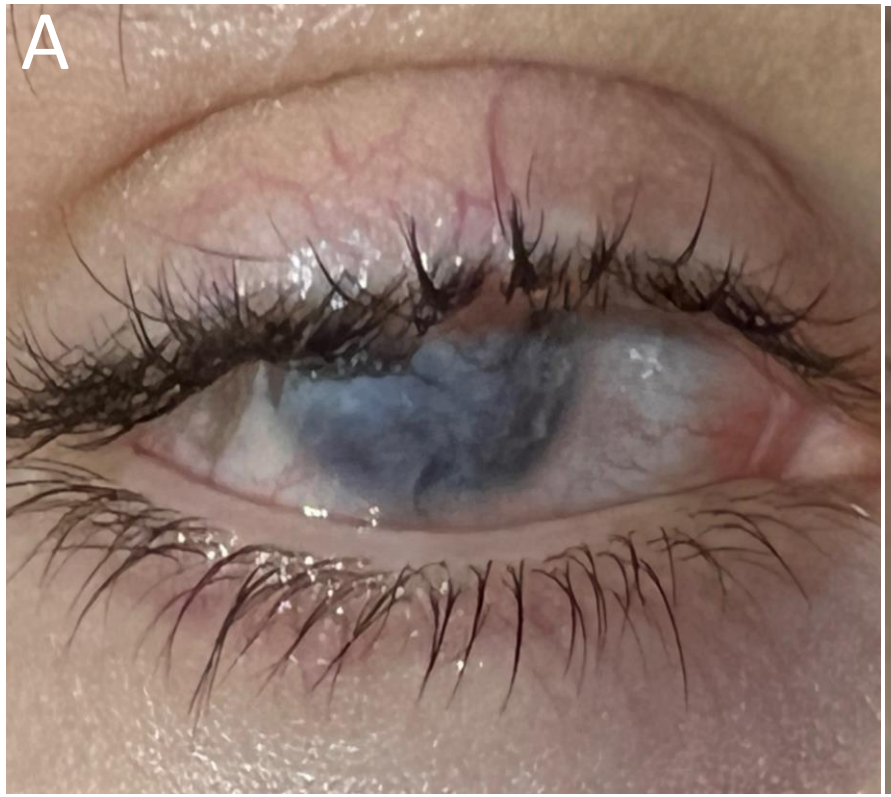
Topical BVEC therapy of the eye

- Surgical symblepharon lysis with pannus removal, was performed on 13 yo with RDEB.
- B-VEC drug product application (5×10^9 PFU/mL) to right eye intraoperatively
- After the surgery, topical B-VEC was applied to eye 3 times/week for the first 2 weeks; then once weekly until the corneal epithelium healed completely

Slit lamp pictures of right eye.

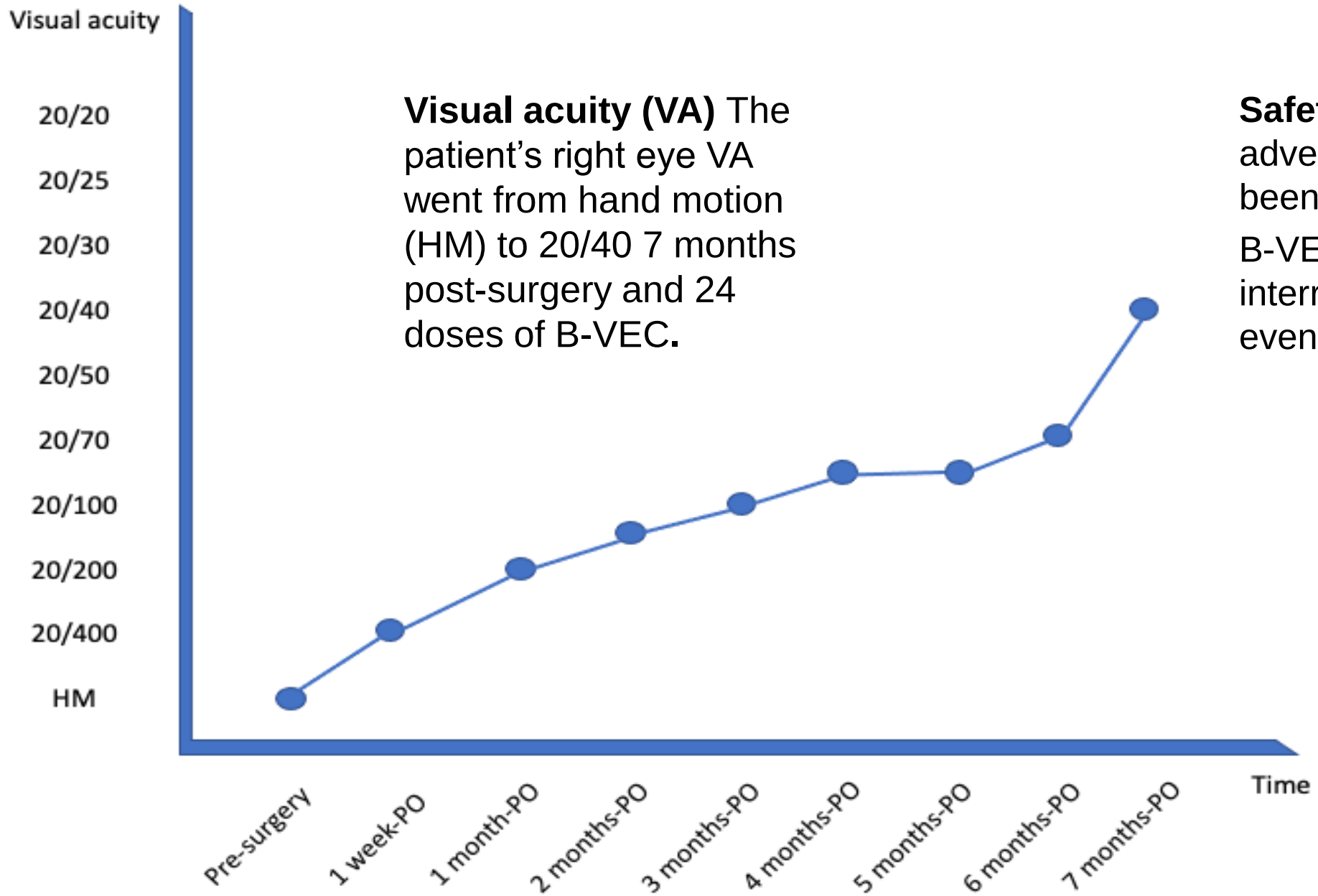
A: Baseline ankyloblepharon.

B: Ocular surface of the right eye 6 months after the surgery and 23 B-VEC applications.



Bascom Palmer Eye Institute
UNIVERSITY OF MIAMI HEALTH SYSTEM

Topical BVEC therapy of the eye - cont.

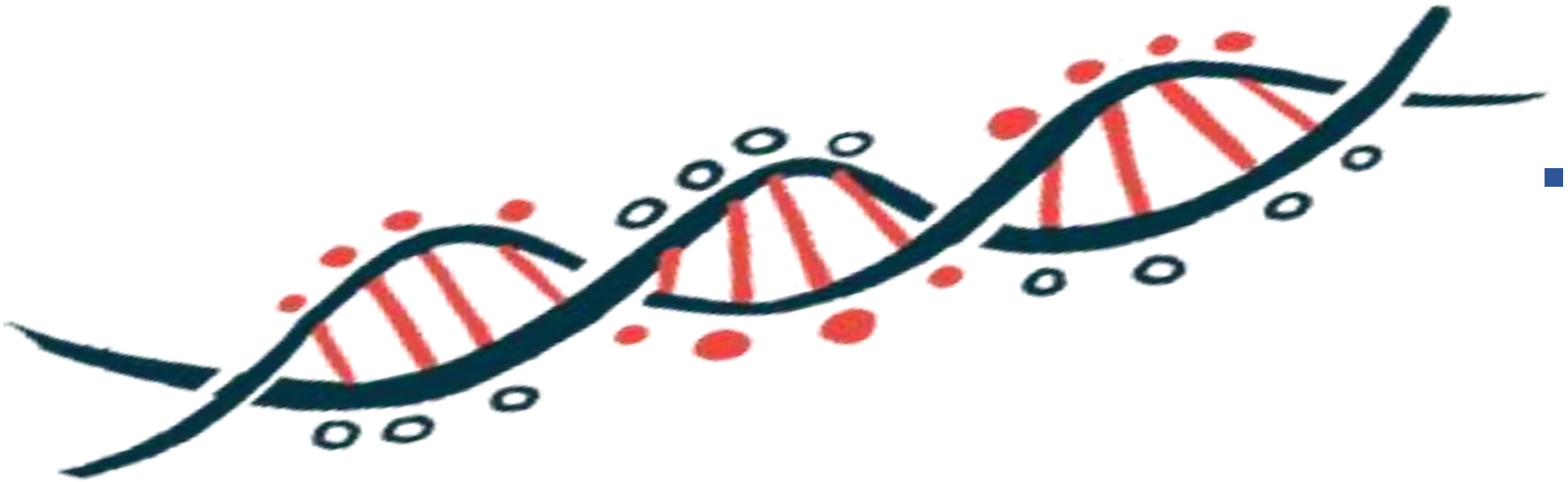


Visual acuity (VA) The patient's right eye VA went from hand motion (HM) to 20/40 7 months post-surgery and 24 doses of B-VEC**.**

Safety: No drug-related adverse events (AE) have been observed.

B-VEC treatment was not interrupted during either event.

Topical BVEC gene therapy: Next steps



- Home therapy
- Further long term studies
- Treatment of mucosa
  - Eye (ongoing studies)
  - Oropharynx
  - Esophagus
  - rectal
- Treatment of hands (ongoing)

Thank you!!!

Topical group

Mercedes Gonzalez
Shireen Guide
Sinem Bagci
Irina Gurevich
Alphonso Sabatar
Brittani Agostini
John Dolorito
Hubert Chen
Gloria Feeney
Surya Chitra
Binoy Kapadia
Molly Steimer
Pooja Agarwal
PeiPei Zhang
Stacie Oliver
Henry Liu
Nicholas Reitze
Nikhil Sarma
Kunju Sridhar
Visesha Kakarla
Vamsi Yenamandra
Mark O'Malley
Marco Prisco
Anastasia McManus
Ilia Antonino
Sara Tufa
Douglas Keene
Andrew South
Suma Krishnan
Peter Marinkovich

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Al Lane
Doug Keene
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Zurab Siprashvili
Ngon Nguyen
Emily Gorel
Kylie Loutit
Kerri Rieger
Peter Lorenz
Louise Furakawa
Peter Marinkovich

And a special thanks to all the wonderful and amazing EB patients who worked with us on these trials !!!

Stanford MEDICINE

Bascom Palmer Eye Institute
UNIVERSITY OF MIAMI HEALTH SYSTEM

Lucile Packard Children's Hospital AT STANFORD

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Abeona THERAPEUTICS

Castle Creek Biosciences

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

EB MRF

EB RESEARCH PARTNERSHIP

debra International