Krystal

Medicines for Rare Diseases –
A Gene Therapy Company

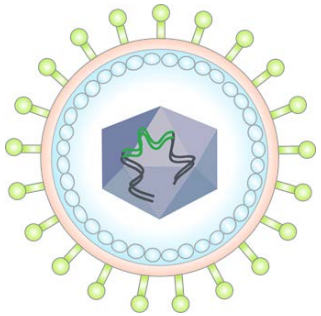
CORPORATE PRESENTATION
Q2 2020

Forward-Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. Any statements in this presentation about future expectations, plans and prospects for Krystal Biotech, Inc. (the “Company”), including but not limited to statements about the development of the Company’s product candidates, such as the future development or commercialization of B-VEC, KB105 and the Company’s other product candidates; conduct and timelines of clinical trials, the clinical utility of B-VEC, KB105 and the Company’s other product candidates; plans for and timing of the review of regulatory filings, efforts to bring B-VEC, KB105 and the Company’s other product candidates to market; the market opportunity for and the potential market acceptance of B-VEC, KB105 and the Company’s other product candidates, the development of B-VEC, KB105 and the Company’s other product candidates for additional indications; the development of additional formulations of B-VEC, KB105 and the Company’s other product candidates; plans to pursue research and development of other product candidates, the sufficiency of the Company’s existing cash resources; and other statements containing the words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “likely,” “will,” “would,” “could,” “should,” “continue,” and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: the content and timing of decisions made by the U.S. Food and Drug Administration, European Medicines Agency and other regulatory authorities; the uncertainties inherent in the initiation and conduct of clinical trials, availability and timing of data from clinical trials; whether results of early clinical trials or studies in different disease indications will be indicative of the results of ongoing or future trials; uncertainties associated with regulatory review of clinical trials and applications for marketing approvals; the availability or commercial potential of product candidates; the ability to retain and hire key personnel; the sufficiency of cash resources and need for additional financing; and such other important factors as are set forth in the Company’s annual and quarterly reports and other filings on file with the U.S. Securities and Exchange Commission. In addition, the forward-looking statements included in this presentation represent the Company’s views as of the date of this presentation. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company’s views as of any date subsequent to the date of this presentation.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Neither we nor any other person makes any representation as to the accuracy or completeness of such data or undertakes any obligation to update such data after the date of this presentation. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

A Leading Gene Therapy Company Focused on Rare Diseases



Platform has generated **two product candidates with clinical PoC**

B-VEC advancing to **Phase 3 pivotal study** in 1H 2020 for Dystrophic epidermolysis bullosa (DEB)

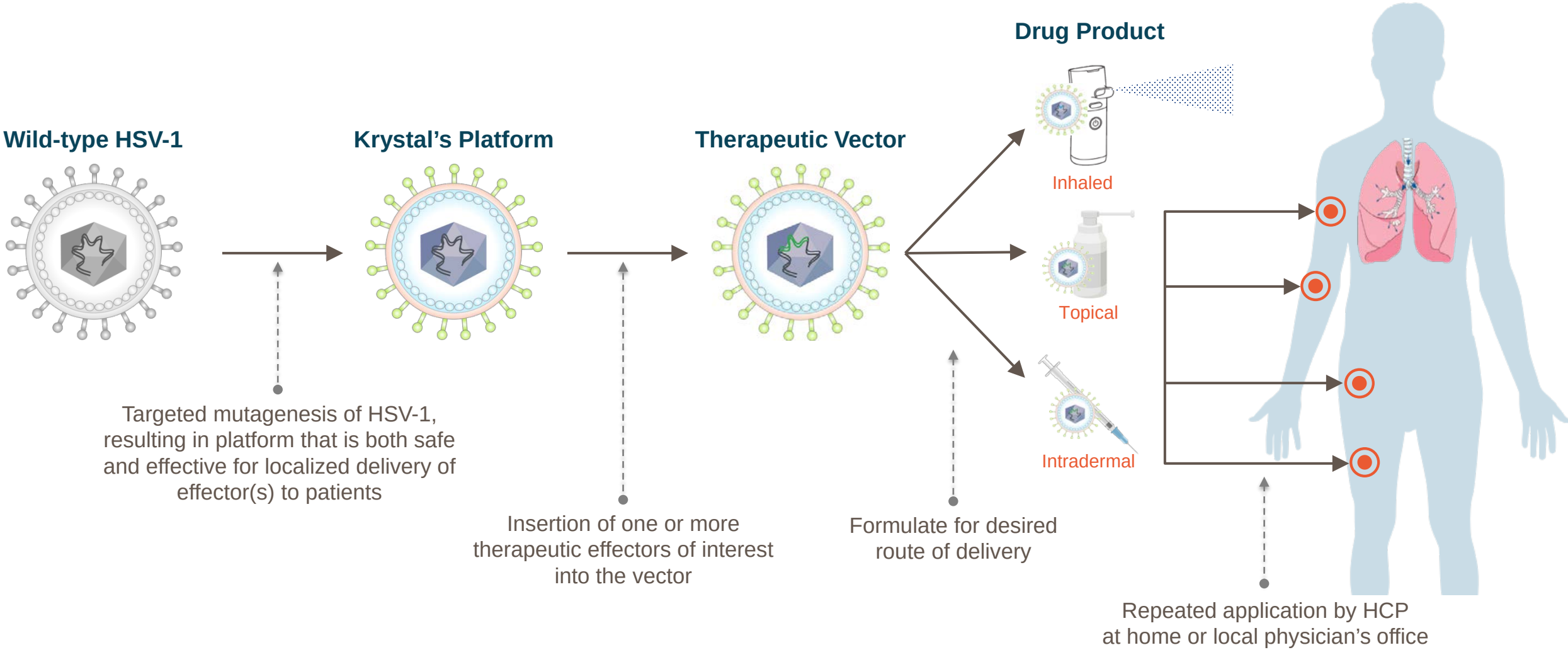
KB105 advancing to **Phase 2 pediatric study** in 2H 2020 for TGM1-deficient autosomal recessive congenital ichthyosis (ARCI)

Filing **two INDs in dermatology** in 2H 2020 and an **IND in Cystic Fibrosis (CF)** in 2021

First **GMP in-house manufacturing facility operational**; second facility expected to be operational in 2022

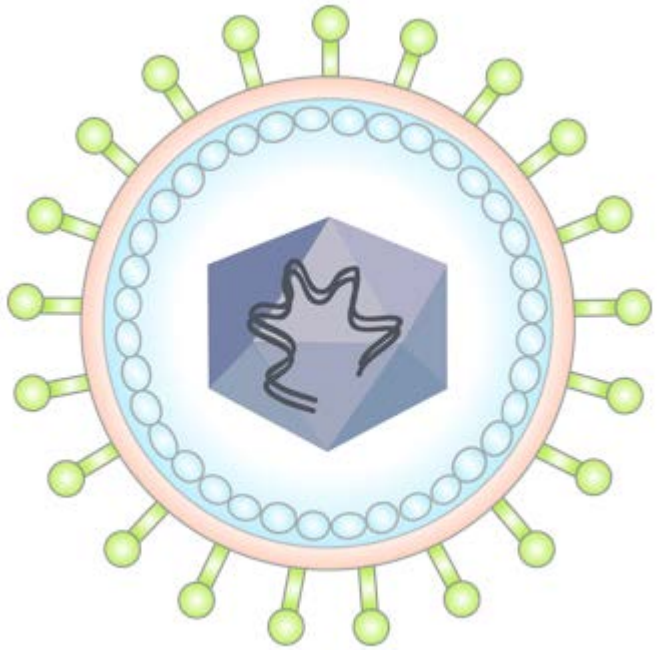
Well capitalized with **$186.7M** as of 3/31/20, prior to the completion of **$125mm public offering** of our common stock on 5/21/20

Krystal's Unique Gene Therapy Approach



Krystal's Platform Technology

Modified Herpes Simplex Virus 1 (HSV-1)



High Payload Capacity (150KB genome)

- Can package one or more copies of large genes (*COL7A1*, *CFTR*) into the vector

High Transduction Efficiency (>90%)

- Minimizes viral shedding and/or systemic vector presence
- Targeted distribution

Non-Integrating and Non-Replicating Vector

- Minimize risk of oncogenesis
- Safe re-administration
- Modified to reduce risk of immune response to vector

Scaled Up In-House GMP manufacturing

- Robust and flexible drug production
- Proven ability to build GMP approved facility (ANCORIS) with future capacity build out (ASTRA)

Krystal's Current Pipeline

Product	Indication	Discovery	Preclinical	Phase I/II	Phase III	Key Upcoming Milestones	WW Rights
B-VEC†¤•Δ‡§	**Dystrophic EB**					**Initiate Pivotal Ph 3 in 1H 2020**	Krystal
KB105†¤•‡	**TGM1-deficient ARCI**					**Initiate Ph 2 in Peds in 2H 2020**	Krystal
KB301	**Aesthetic Skin Conditions**					**File IND in 2H 2020**	Krystal
KB104	**Netherton Syndrome**					**File IND in 2H 2020**	Krystal
KB407	**Cystic Fibrosis**					**File IND in 1H 2021**	Krystal
KB5XX	**Chronic Skin Diseases**						Krystal

†: FDA Orphan Drug Designation;
¤: FDA Rare Pediatric Disease Designation;
•: Fast-track Designation;
Δ: FDA RMAT designation;
‡: EMA Orphan Drug Designation;
§: EMA PRIME Designation.

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Different Routes of Administration to Tackle Spectrum of Diseases and Conditions

1. Topical

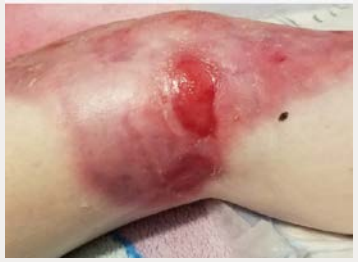
Indications: Dystrophic Epidermolysis Bullosa (DEB); Autosomal Recessive Congenital Ichthyosis (ARCI); Netherton Syndrome (NS); Atopic Dermatitis

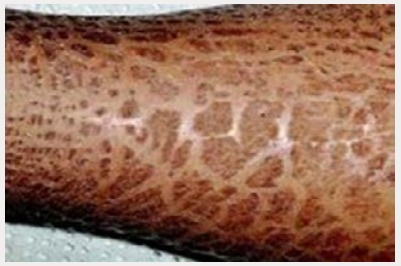
Skin Integrity:

Blistered, open skin (DEB)

Non blistered, but with breaks in skin barrier (e.g., ARCI)

Intact skin with underlying issues (Aesthetics)





Effectors: *COL7A1* (type VII collagen); *TGM1* (transglutaminase-1); *SPINK5* (serine protease inhibitor kazal-type 5); Anti-inflammatory antibodies and antibody fragments

2. Intradermal

Indications: Hidradenitis Suppurativa (HS), aesthetics

Effectors: Collagens; Anti-inflammatory antibodies and antibody fragments

3. Inhalation

Indications: cystic fibrosis, alpha 1 antitrypsin deficiency

Effectors: *CFTR*, *SERPINA1*

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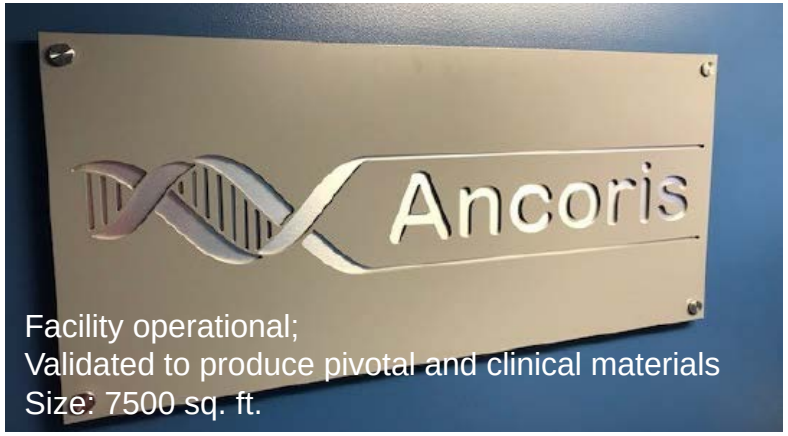
Krystal's Core Competency: CMC/Manufacturing

Established process conducted at Krystal's end-to-end GMP facility (Ancoris)

- Maintains control of IP/trade secrets relating to manufacturing process
- Adheres to internal process and production schedules, avoiding use of high demand gene therapy CMOs



Facility operational;
Validated to produce pivotal and clinical materials
Size: 7500 sq. ft.

Upstream Production Process

- Proprietary engineered vectors and complementary/supporting cell lines developed in-house are used in established methods for production of consistent batches
- Scalable from clinical phase to commercial


ASTRA (rendering)
Operational in 1H 2022
Size: 100,000 sq. ft.

Downstream Purification Process

- Work conducted in an aseptic closed system process
- Process accommodates ever-expanding vector pipeline with minimal redevelopment effort between product candidates
- Compliant to global regulatory requirements

B-VEC (previously KB103)*

USAN & INN: *beremagene geperpavec*

For treatment of dystrophic epidermolysis bullosa (DEB)

* RMAT designation;

PRIME Eligibility;

Fast Track Designation Granted;

Orphan Drug Designation in US and EU;

Rare Pediatric Disease Designation in US;

Eligible for Priority Review Voucher.

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Dystrophic Epidermolysis Bullosa (DEB)

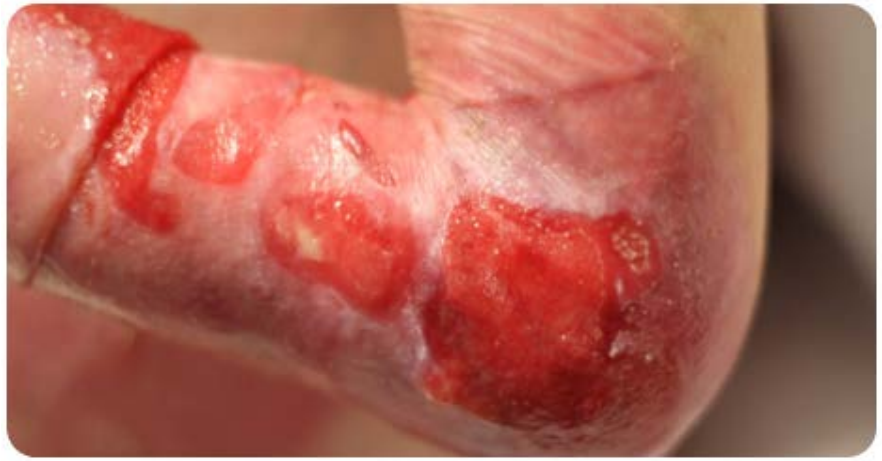
“Butterfly Children” is used to describe young DEB patients because their skin is as fragile as a butterfly’s wings

Dystrophic Epidermolysis Bullosa

A rare, genetic connective tissue disease that causes skin to tear or blister from minor contact

Caused by a mutation in the *COL7A1* gene that codes for the COL7 protein

Without COL7 the epidermis does not anchor to the dermis



Epidemiology

Prevalence: Up to 125,000 people are affected by DEB worldwide[1]

Incidence: The incidence of DEB is 6.5 per million births in the US[2]

Current Standard of Care

There are no approved treatments for DEB

Existing therapies limited to expensive and time-consuming palliative treatments

Palliative treatments cost $200k – $400k annually[3,4]

1. DEBRA International, http://www.debra-international.org/epidermolysis-bullosa/causes-and-subtypes.html; http://www.debra-international.org/what-is-eb/causes-and-subtypes/deb.html
2. Pfendner EG, Lucky AW. Dystrophic Epidermolysis Bullosa. 2006 Aug 21 [Updated 2015 Feb 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet].
3. Rashidghamat E., Mellerio J.E., Management of chronic wounds in patients with dystrophic epidermolysis bullosa: challenges and solutions, Chronic Wound Care Management and Research Volume 2017:4, 45-54
4. GENEGRAFT Report Summary. (2015, February 16). Retrieved December 13, 2016, from http://cordis.europa.eu/result/rcn/156078_en.html

Simple, Painless and Easy to Administer

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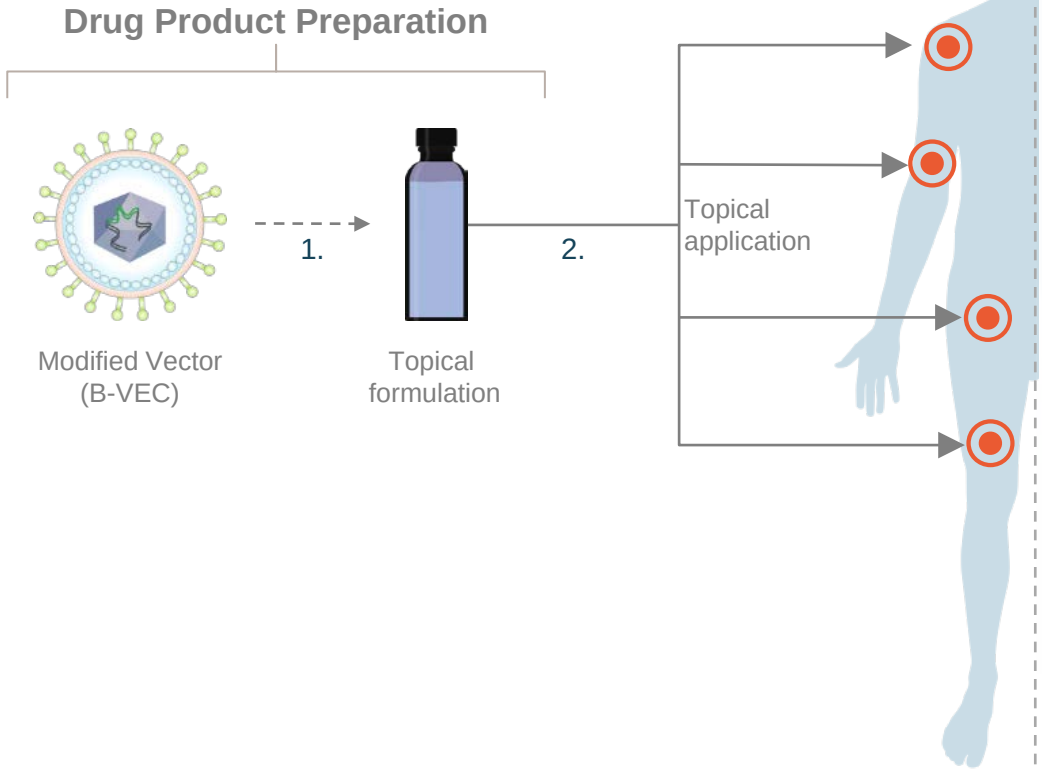
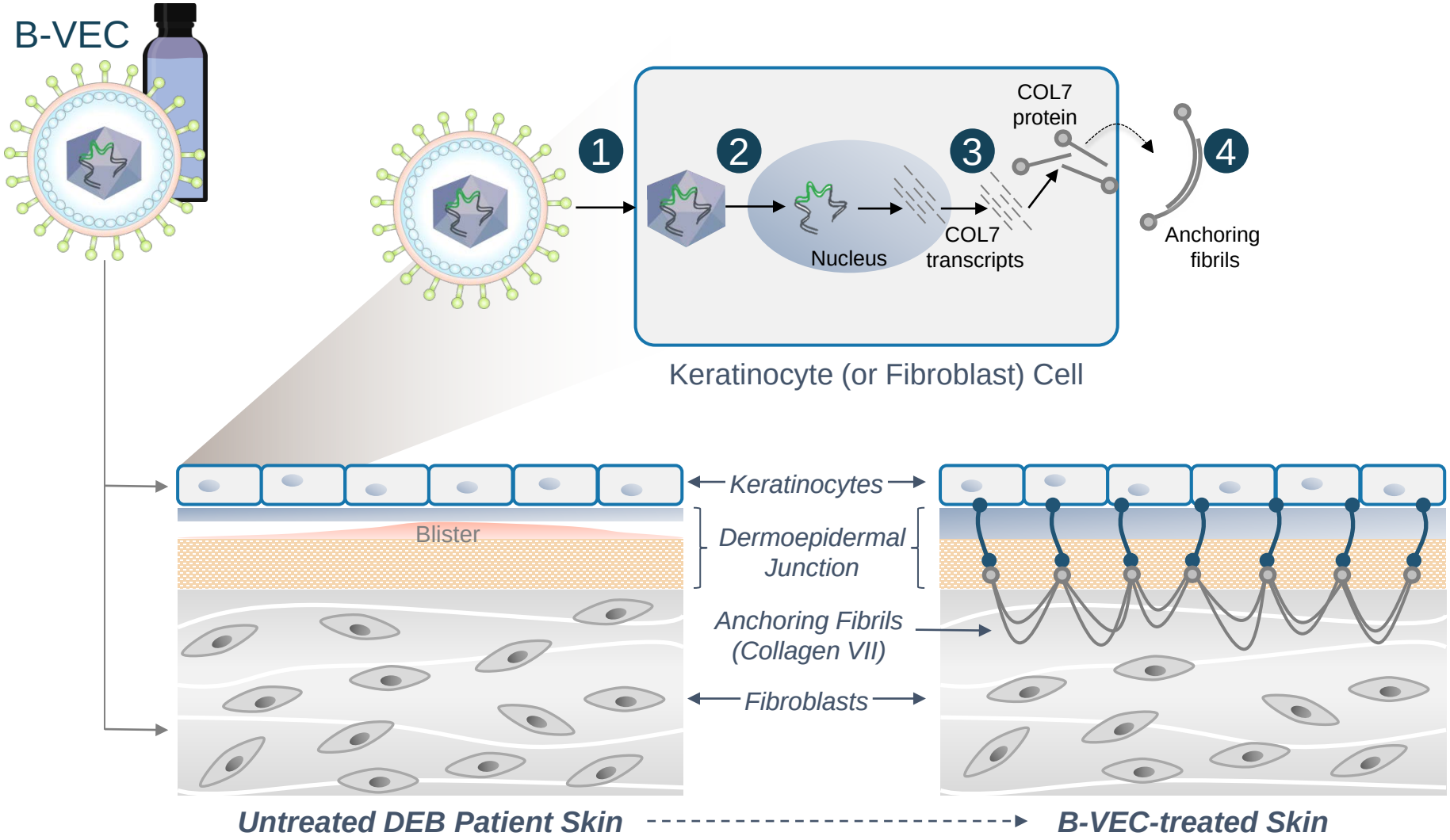
Non-Invasive
Modified HSV-1 Therapy



Benefits of Krystal's approach:

- Topical application that is ready for use for the treatment of any wound
  - Non-invasive
  - Speed to wound healing
  - Adaptable to treat wounds regardless of size
- Administration by an HCP in an outpatient setting
  - No hospitalizations required
  - Does not need expensive, invasive, and time-consuming procedures or sophisticated medical teams
- Taking gene therapy closer to the patient
  - Minimizes patient travel

B-VEC Mechanism of Action



1. B-VEC enters the compromised skin of DEB patients and transduces both keratinocytes and fibroblasts
2. The drug enters the nucleus of transduced cells and the vector genome is deposited (episomally)
3. *COL7A1* transcripts are generated, which allows the cell to produce and secrete functional COL7 protein
4. The secreted COL7 protein assembles into anchoring fibrils which hold the epidermis and dermis together

B-VEC Clinical Data

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Summary of Phase 1/2 Study Design

- This study was an intra-patient comparison of wounds randomized to receive either topical B-VEC or placebo.
- In Phase 1 (2 patients) one wound was administered B-VEC and one wound was administered placebo.
- In Phase 2 (6 patients, 4 in Phase 2A and 2 in Phase 2B), 2 wounds were administered B-VEC and one wound was administered placebo.
- Three-month trial plus long term imaging post-study.
- Dosing range in combined study was 1e8 - 8e8 pfu/wound/administration.
- Safety was assessed through AEs, including clinically significant changes in laboratory results, vitals, and physical exam findings.
- Viral shedding was analyzed through the collection of blood, urine, and skin swabs, and antibodies to HSV and COL7 were analyzed through collection of serum.

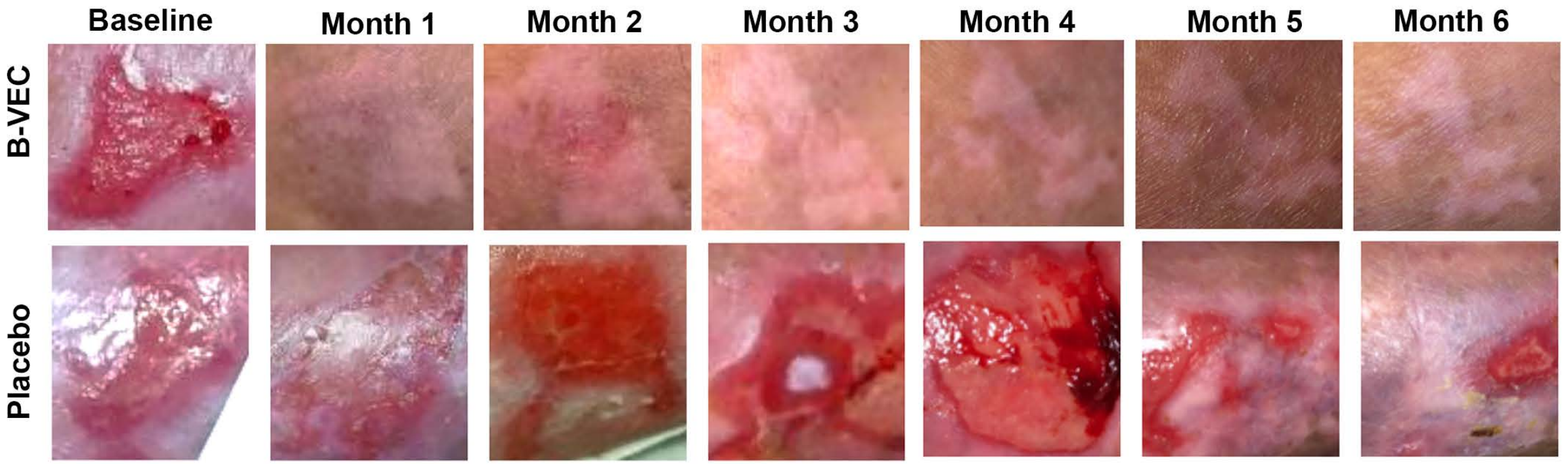
B-VEC Safety Update in Wounds with Topical Application

B-VEC continues to be well tolerated to date following first and repeat dose

- No treatment-related adverse events (serious or otherwise) were reported.
- No immune response or blistering observed around the sites of administration following first and repeat dose.
- Blood and urine samples collected throughout the study revealed:
  - No systemic viral shedding
  - No adverse events associated with routine labs (chemistry and hematology)
  - Some patients had baseline COL7 and HSV1 antibodies which did not impair efficacy or tolerance of therapy

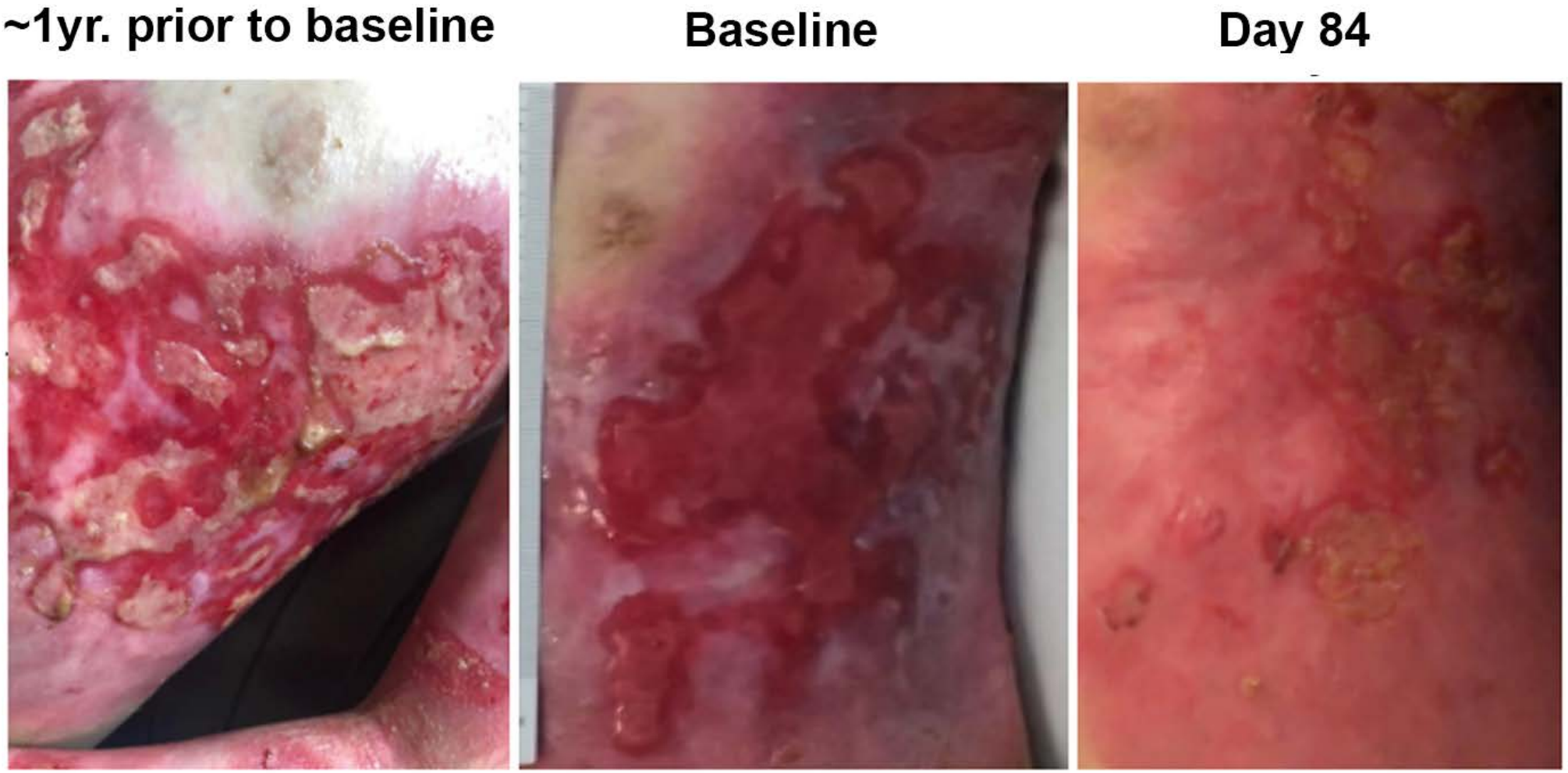
B-VEC Study: Illustrative Wound Healing (Pt. 09)

Sustained closure of B-VEC treated wound compared to the dynamic nature of the placebo wound



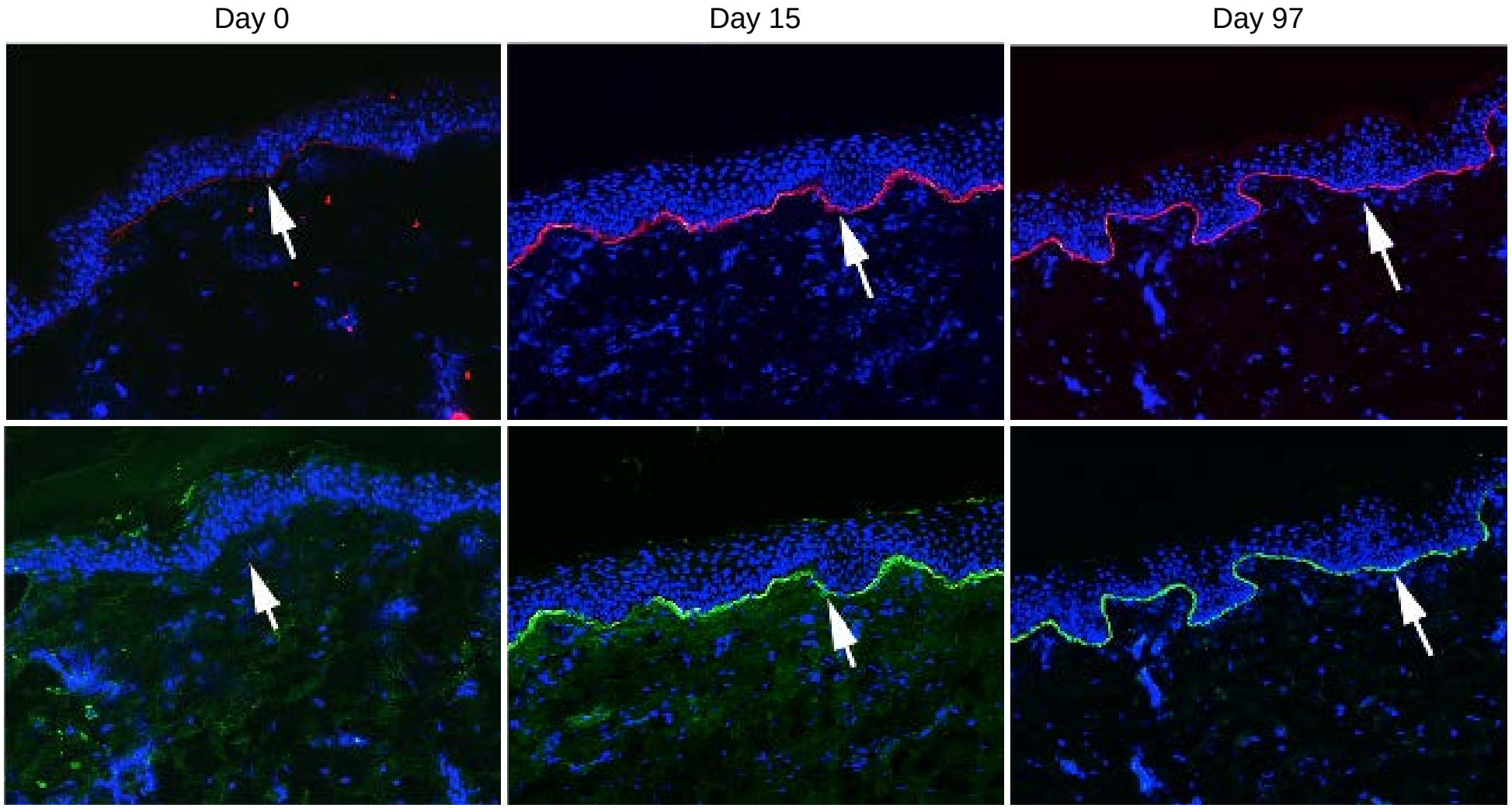
B-VEC Study: Illustrative Chronic Wound Healing (Pt. 12 - Age 11)

Large chronic wound present for > 5 years covering the left side of patient's torso



Linear Full-Length COL7 Expression Following B-VEC Therapy: Pt. 10

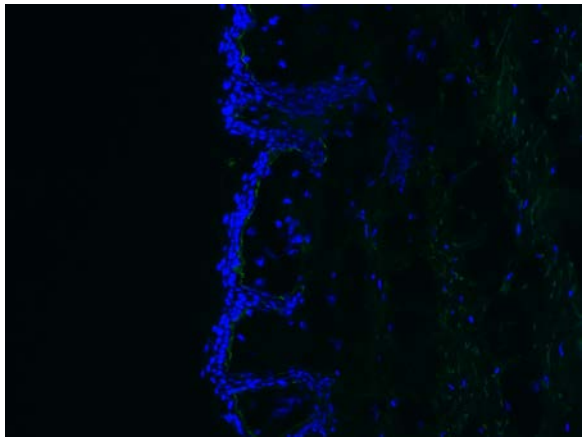
Baseline, Days 15 and 97 COL7 expression using NC1 and NC2 specific antibodies



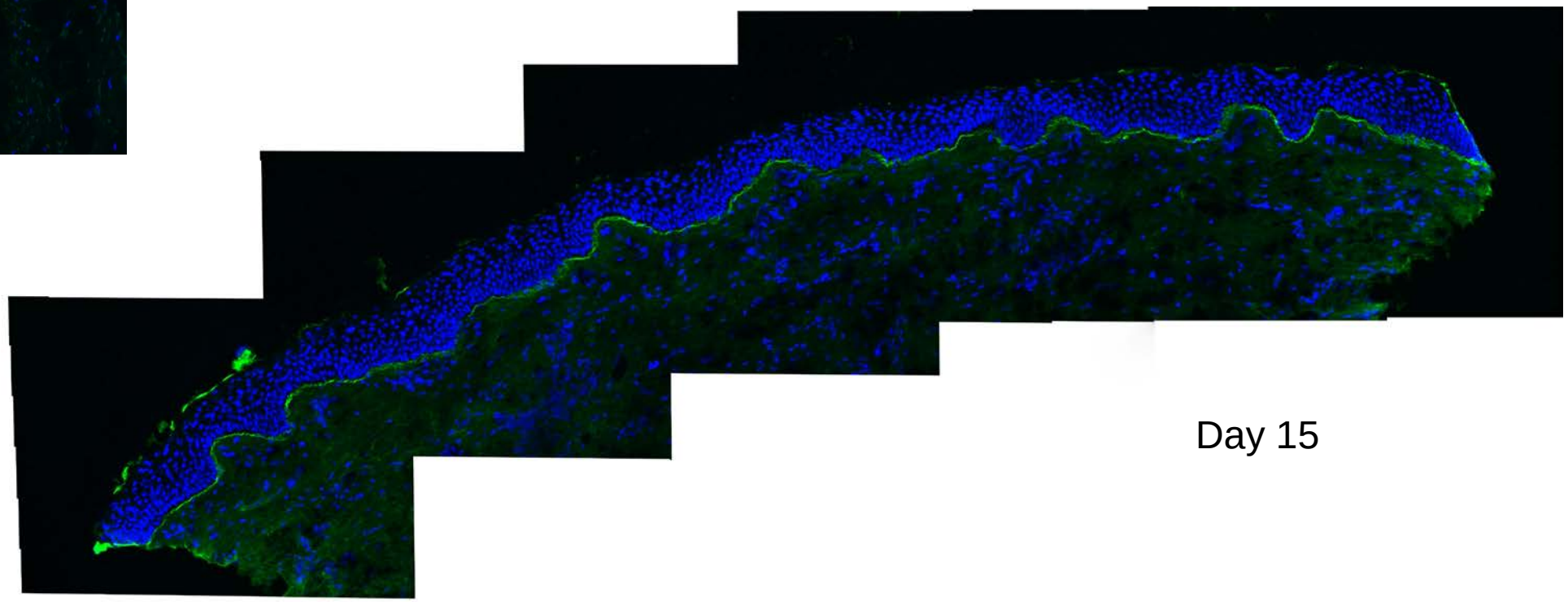
Arrows indicate basement membrane zone

Tile Analysis Demonstrates Long Stretches of Linear Full-Length COL7 Expression Following B-VEC Therapy: Pt. 10

Baseline and Day 15 COL7 expression using NC2 specific antibody



Baseline



Day 15

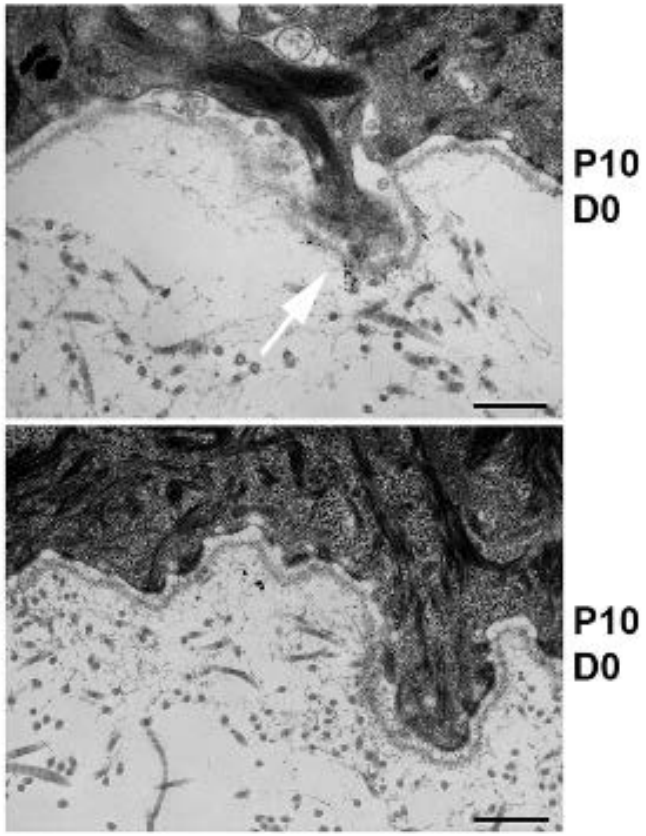
Full-Length COL7 Promotes the Formation of Mature Anchoring Fibrils Following B-VEC Therapy

Baseline

Minimal baseline expression of NC1 (arrow)

Absent baseline expression NC2

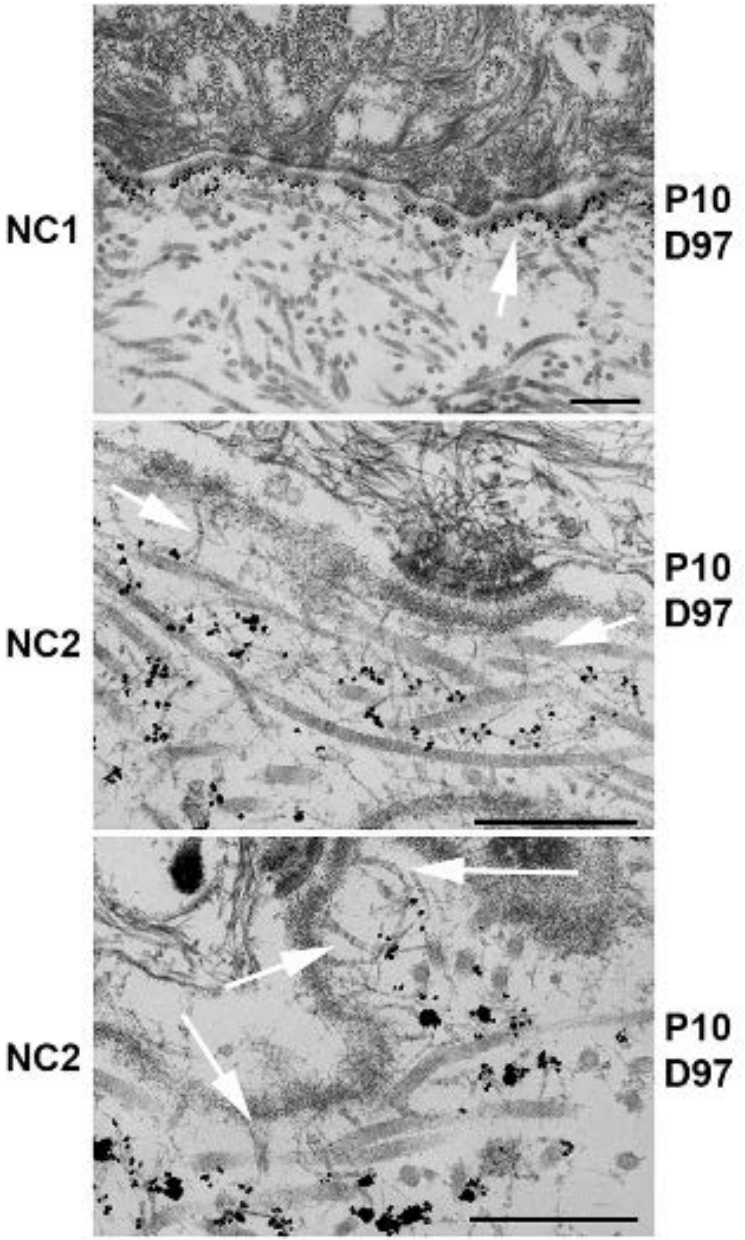
Absent anchoring fibrils



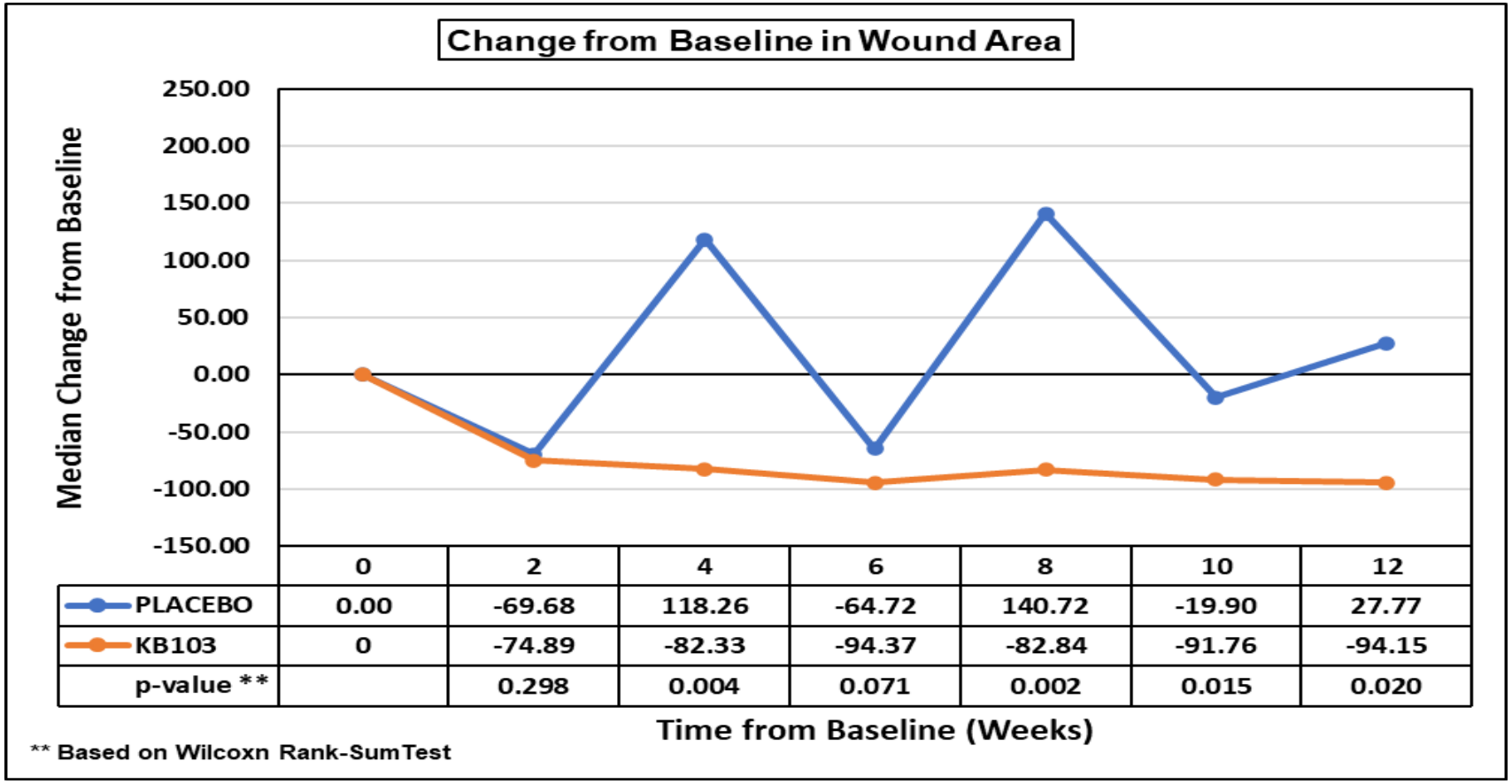
Increased expression of NC1 (arrow)

Increased expression NC2 (black dots)

Robust, mature anchoring fibrils (arrows)



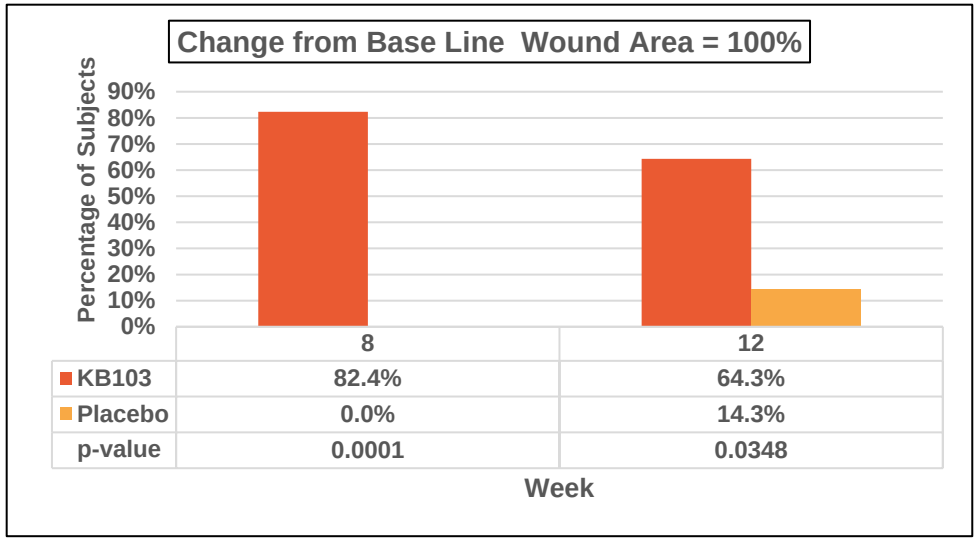
Median Change in Wound Area

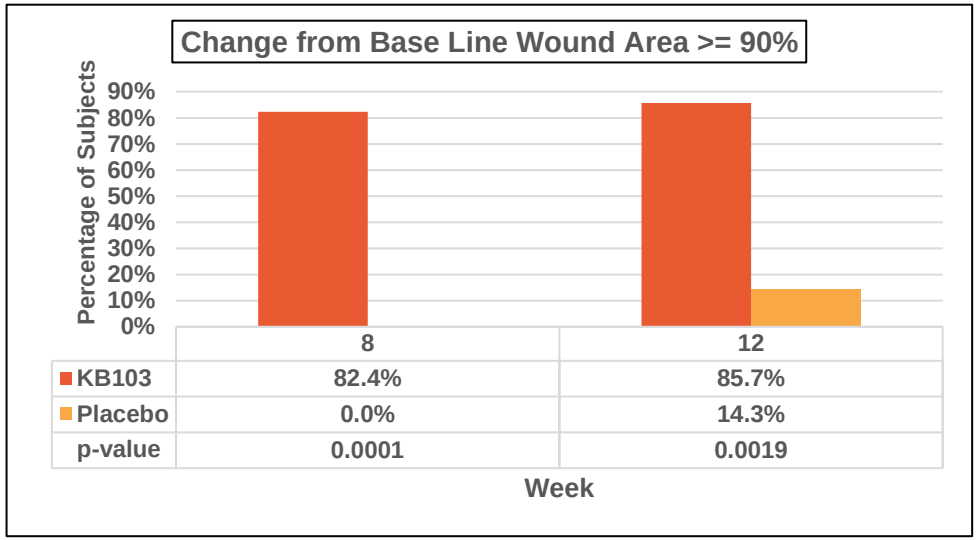


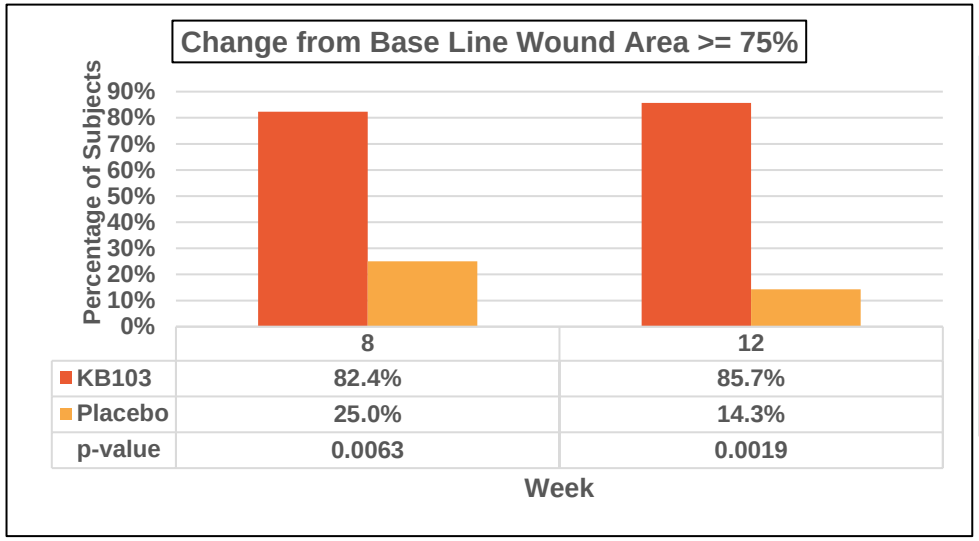
	0	2	4	6	8	10	12
PLACEBO	0.00	-69.68	118.26	-64.72	140.72	-19.90	27.77
KB103	0	-74.89	-82.33	-94.37	-82.84	-91.76	-94.15
p-value **		0.298	0.004	0.071	0.002	0.015	0.020

Statistically Significant (p-value < 0.05) Reduction in Wound Area Achieved in Weeks 8,10, and 12

Wound Closure Active vs. Placebo at Week 8 and 12







Wound Closure Response is Statistically Significant (p-value < 0.05) For All Endpoints

p-values are based on Cochran-Mantel Haenszel (CMH) Test Without Adjusting for Week-to-Week Placebo Variability

In Summary

- B-VEC is being developed as a topical gel to treat patients with dystrophic epidermolysis bullosa, and is designed to be applied by a health care professional.
- B-VEC continues to be well tolerated following initial and repeated dosing; no treatment-related adverse events (serious or otherwise) were reported
- No immune response or blistering observed around the sites of administration following first and repeat doses, supporting B-VEC's amenability for repeated administration
- 9 out of 10 wounds closed completely (100% closure) following initial administrations of B-VEC
  - The average time to 100% wound closure on the 9 B-VEC treated wounds was 17.4 days (median 14 days)
  - The average duration of wound closure on the 9 B-VEC treated wounds at last measured timepoint was 113 days (median 110 days)
- Clinical data to date shows that B-VEC heals both chronic and recurrent wounds and separates significantly from placebo in wound closure between Weeks 8 through 12

KB105*

For the treatment of Autosomal Recessive Congenital Ichthyosis associated with TGM1

* Orphan Drug Designation in US and EU;

  Rare Pediatric Disease Designation in US;

  Fast Track Designation Granted;

  Eligible for Priority Review Voucher.

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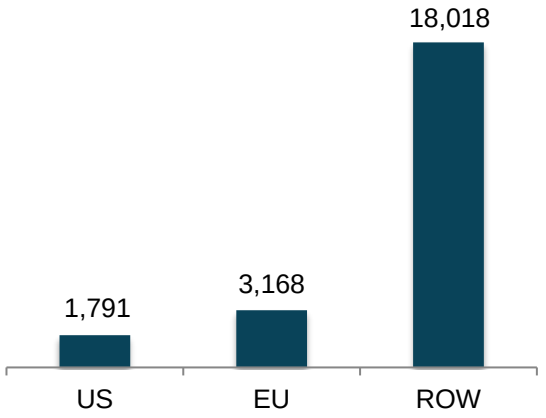
ARCI Associated With TGM1

Autosomal Recessive Congenital Ichthyosis (ARCI) associated with TGM1

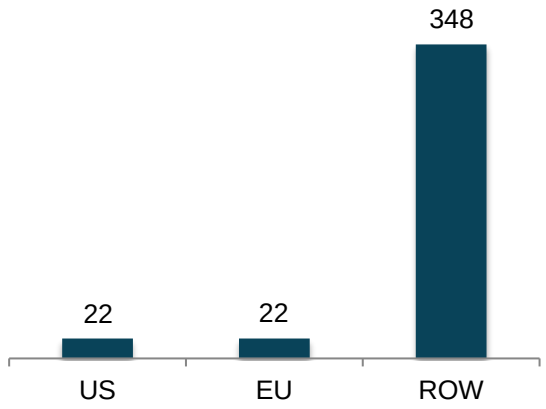
A condition characterized by thick dry scaly skin, increased trans-epidermal water loss (TEWL), risk for dehydration, sepsis, skin malignancies, *etc*.

Caused by a mutation of TGM1 gene required for epidermal barrier formation

ARCI Prevalence[1-8]



ARCI New Cases/Year



Current Standard of Care

There are no approved treatments for ARCI associated with TGM1

Existing approaches limited to time-consuming palliative treatments

1. Rodriguez-Pazos et al. *Actas Dermosifiliogr.* 2013 May;104(4):270–284;
2. Dreyfus et al. *Orphanet J Rare Dis.* 2014 Jan 6;9:1;
3. Hernandez-Martin et al. *J Am Acad Dermatol.* 2012 Aug;67(2):240–244;
4. Pigg et al. *Eur J Hum Genet.* 1998 Nov-Dec;6(6):589–596.
5. Pigg et al. *Acta Derm Venereol.* 2016 Nov 2;96(7):932–937;
6. Orphanet;
7. Foundation for Ichthyosis & Related Skin Types (FIRST);
8. National Organization for Rare Disorders (NORD).

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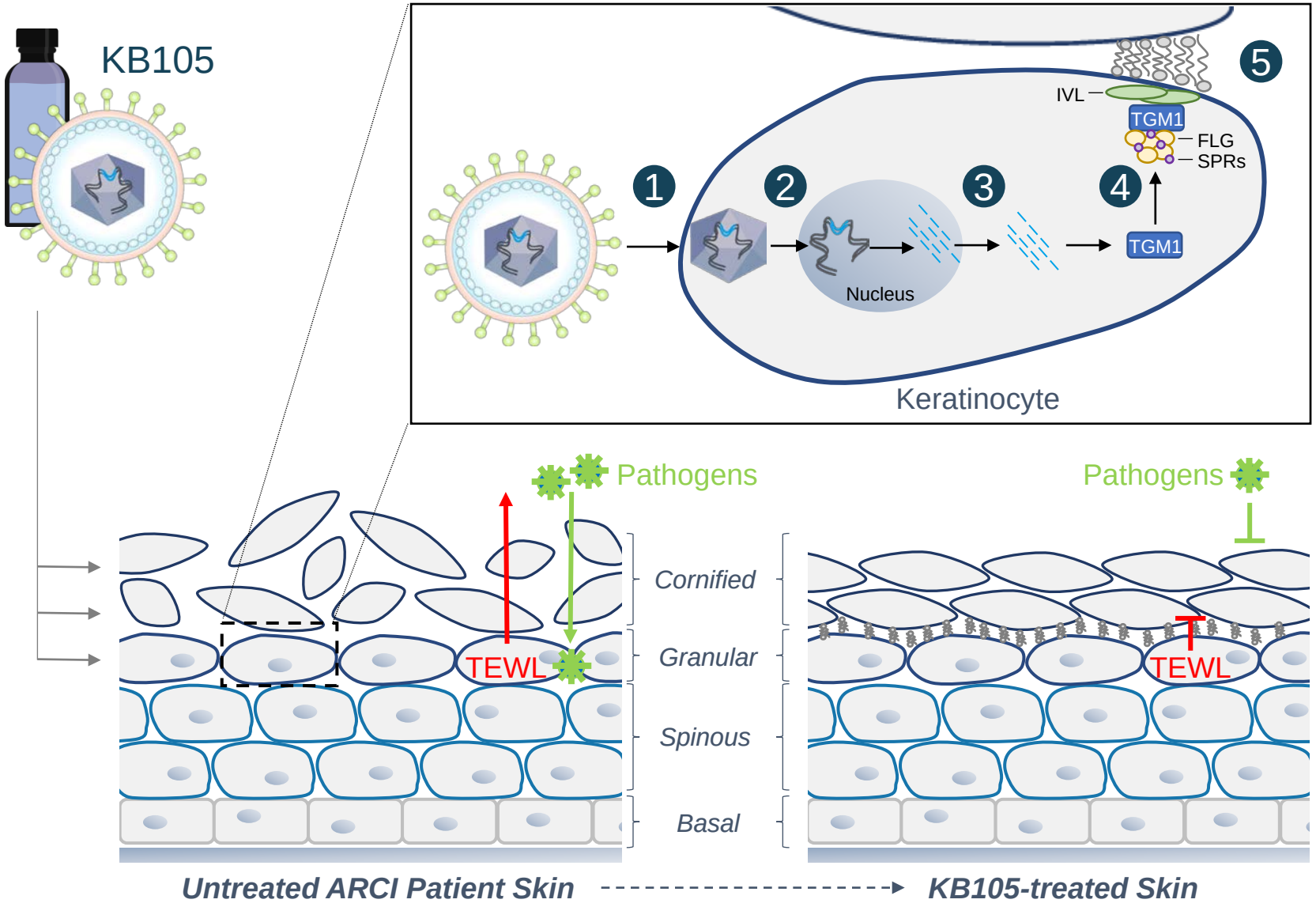
KB105 Mechanism of Action



1. KB105 enters permeabilized skin and transduces keratinocytes (native TGM1-producing cells)
2. KB105 is transported into the nucleus of transduced cells and the vector genome is deposited (episomally)
3. *TGM1* transcripts are generated, which allows the cell to produce functional TGM1 protein that localizes to the cell membrane
4. TGM1 crosslinks target proteins (*e.g.,* filaggrin (FLG), involucrin (IVL), small proline-rich proteins (SPRs)) to aid in the formation of the cornified cell envelope
5. This layer, known as the stratum corneum, acts as a mechanical barrier to protect against transepidermal water loss (TEWL) and entry of infectious agents

KB105 Clinical Data

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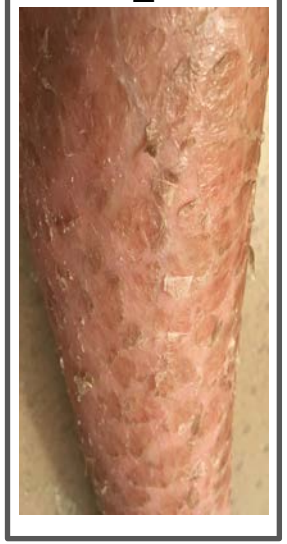
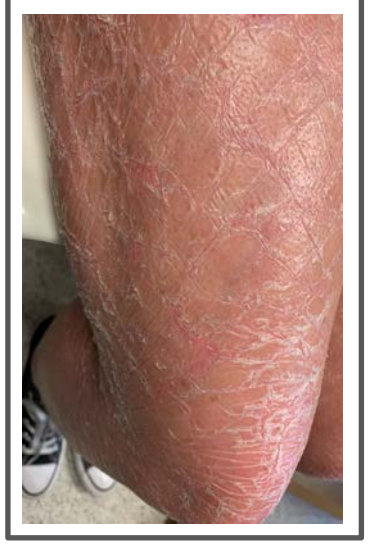
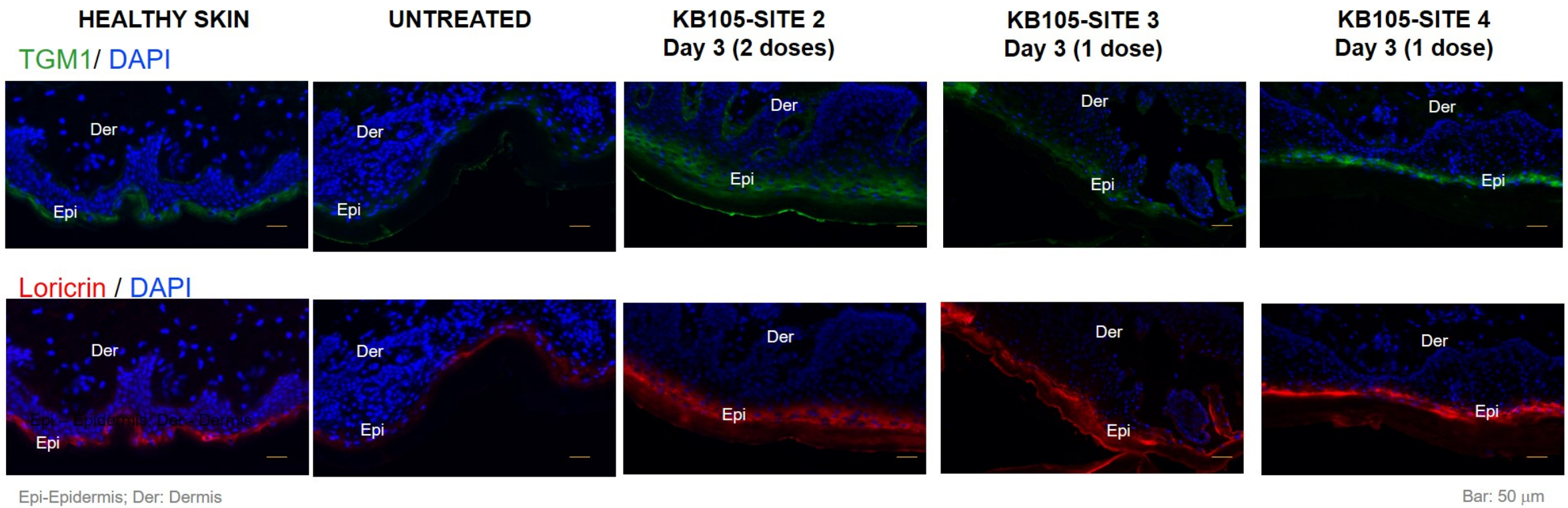
Patient Demographics and Disease Severity

Subject	Age	Gender	Genotype	Medication
1	39	Male	TGM1 c.430 G>A p.G144R & TGM1 c.456_458delCCT p.L153del	35mg oral acitretin (retinoid) daily
2	24	Female	TGM1 c.2060 G>A p.R687H	None
4*	20	Female	c.2526 A>G and c.2391 T>C	None

	1	2	4
			
IGA: Disease Severity	**4**	**3**	**3**

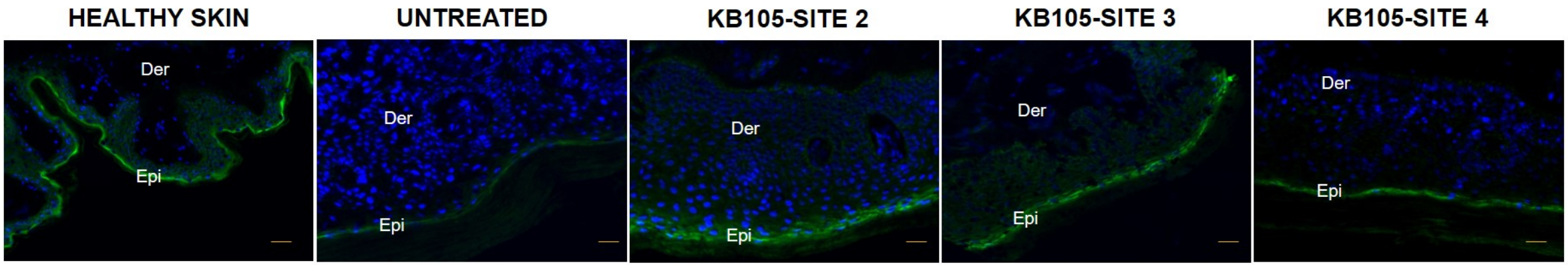
*Subject 4 enrolled but could not keep return visits

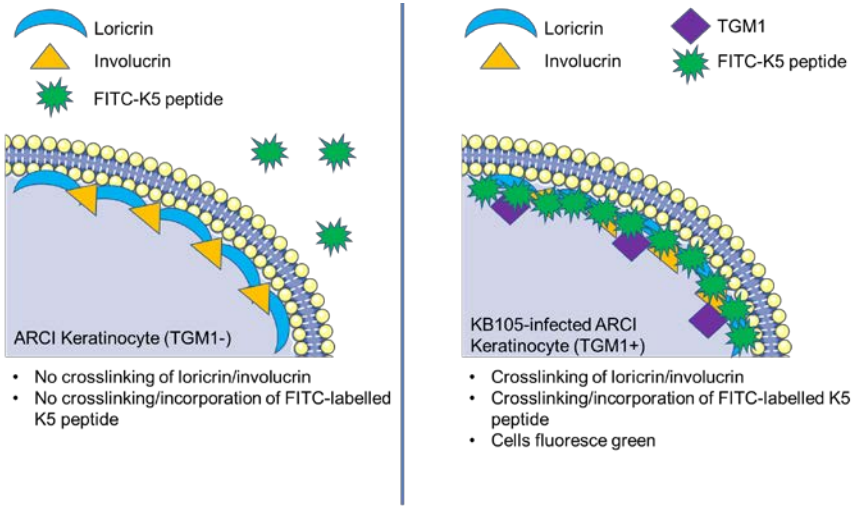
Subject 1: Treatment Restored TGM1 Expression to Normal Levels



- Subject showed no TGM1 expression in untreated area
- TGM1 expression was restored in <u>all three treated sites</u> within 48-hours
- TGM1 colocalized with its substrate, Loricrin, in the epidermis

Subject 1: TGM1 Expression Correlated with Increased *In Situ* Activity





- TGM1 activity was detected by an *in situ* fluorescent enzymatic assay that specifically detects TGM1 function*

*TGM2 inhibitor added to inhibit non-specific detection of TGM2 function

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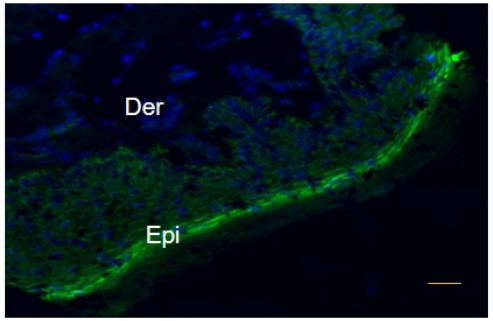
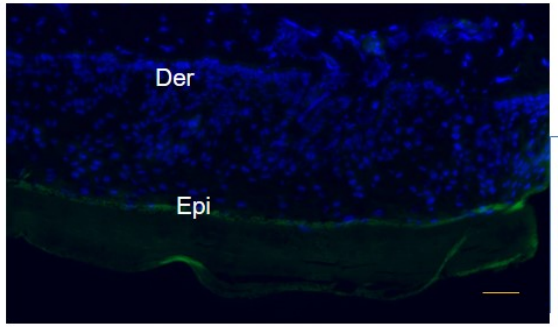
Subject 1: KB105 Was Successfully Repeat Administered Multiple Times

Subject 1: TGM1 levels decline in ~ 2 weeks but are successfully restored by retreatment

Site 2 - Dosing on **D1** and ~~**D2**~~ only

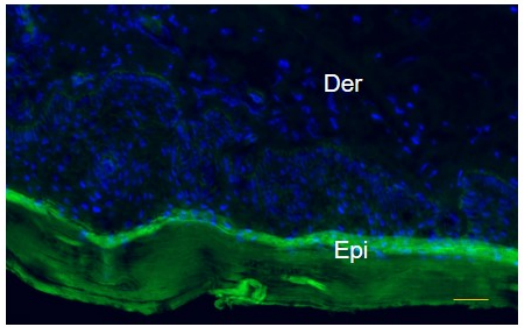


TGM1 Activity restored
Day 3



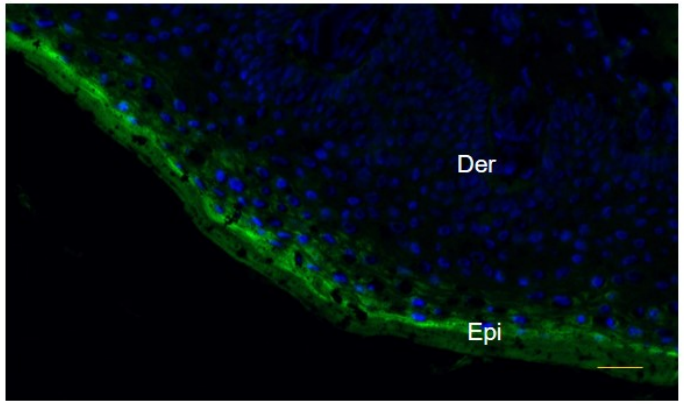
Activity declines to baseline levels
Day 15

Retreatment on **Day 15**



Activity increases to normal levels
Day 16

Retreatment on **Day 36**



Bar: 50 μm

Day 43
Activity persists 7 days later

Epi-Epidermis;
Der: Dermis

- Re-treatment on D15 and D36 boosted activity to normal levels
- Expression levels correlated with changes in functional activity (not shown here)

Summary and Lessons Learned

- Repeat dosing with KB105 was well-tolerated with **no drug related AEs and no immune response to HSV or TGM1**
- **No vector shedding detected in swabs, blood or urine** in all three patients
- KB105 treatment **restored functional TGM1 protein expression and activity** in all treated sites
- **KB105-expressed TGM1 was correctly localized in the epidermis**, colocalizing with Loricrin, and was functionally active
- qPCR, IF, and in situ analyses demonstrated **similar delivery efficacy of TGM1 DNA from single and repeat administration**
- Similar delivery efficacy with and without microneedling, so no microneedling required in future studies
- Phenotypic evaluation limited by small treatment areas, but KB105 treated areas showed reduced reversion to ichthyotic scaling phenotype

KB407

For the treatment of cystic fibrosis

Krystal

Cystic Fibrosis

Most common inherited genetic disorder in the United States

Cystic Fibrosis (CF)

Caused by mutations in the *CFTR* gene encoding the protein cystic fibrosis transmembrane conductance regulator (CFTR).

CFTR is a transmembrane anion channel expressed on the surface of epithelial cells; responsible for maintaining proper fluid transport.

Disease Physiology

Loss of CFTR function causes acidification and mucus accumulation in the lungs, provoking recurrent lung infections, uncontrolled inflammation, and bronchiectasis.

CF comprises a multiorgan pathology; however, primary cause of morbidity and mortality is progressive lung destruction.

Epidemiology of cystic fibrosis[1]

Patient Registries[2]

>30,000 patients with CF in the U.S.

~1,000 new cases of CF diagnosed each year in the U.S.

>70,000 patients with CF worldwide

1: World Health Organization (2004). "The molecular genetic epidemiology of cystic fibrosis".
2: Cystic Fibrosis Foundation Patient Registry.

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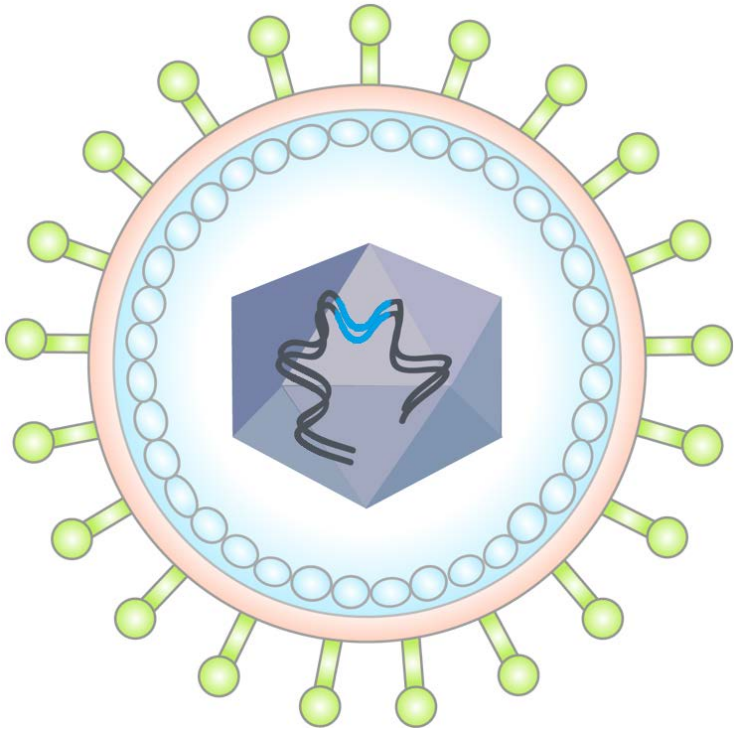
CF Gene Therapy

- Gene therapies have been tested in more than 25 clinical trials enrolling >470 patients
  - Viral (adenovirus and AAV) and non-viral (DNA plasmids and stabilized mRNA)
  - Past approaches suffer from some combination of physical limitations for large cargo, low efficiency of gene transfer, toxicity, immune intolerance, product instability, and burdensome delivery
- Ideal gene therapy candidate:
  - Accommodates large genes and necessary regulatory elements
  - Is amenable to rapid, non-invasive inhaled administration
  - Natural tropism to apical membrane of polarized epithelial cells
  - Non-cytotoxic
  - Non-immune stimulating
  - Safe and effective for repeated administration in highly inflammatory environments

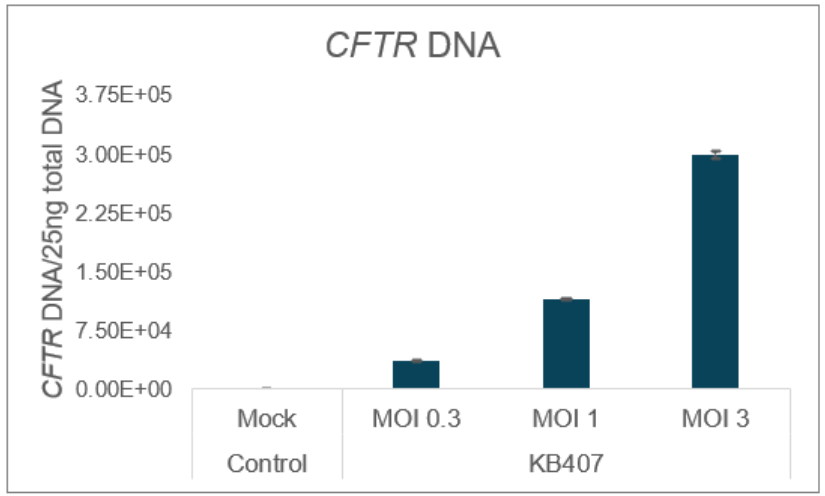
KB407

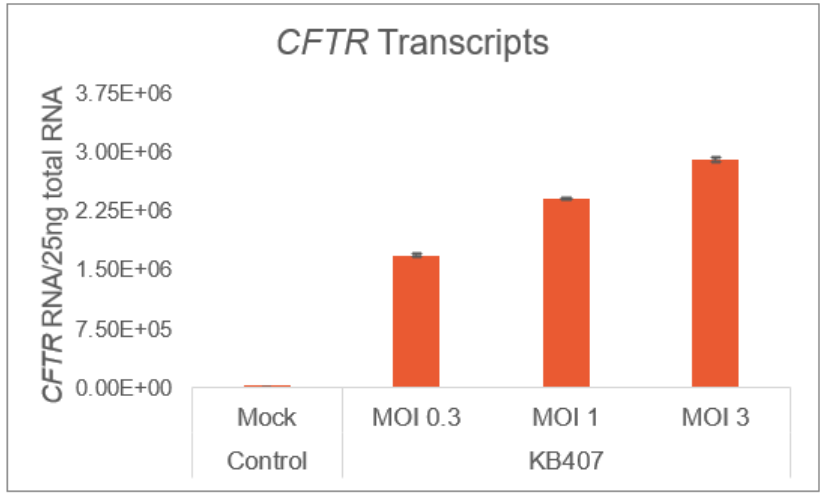


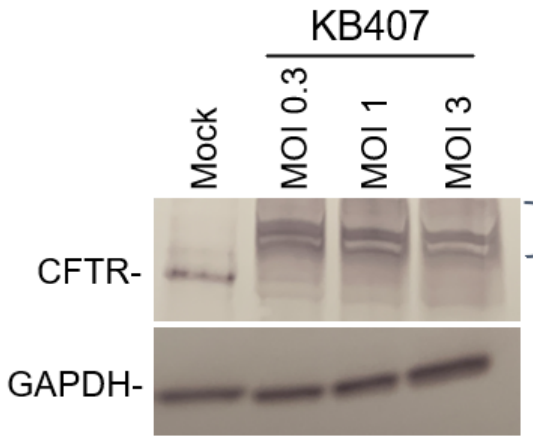
A replication-incompetent HSV-1 vector expressing full-length human CFTR for the treatment of cystic fibrosis

KB407 in CF Patient-Derived Small Airway Epithelial Cells

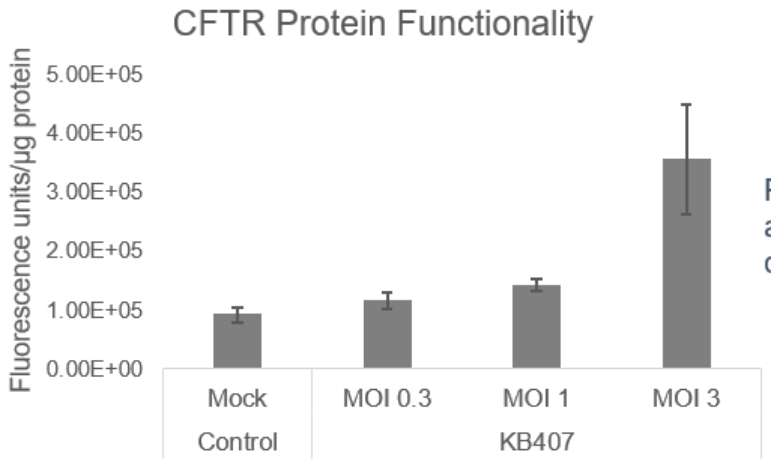
Robust, dose-dependent CFTR expression and functional correction in 2D cultures







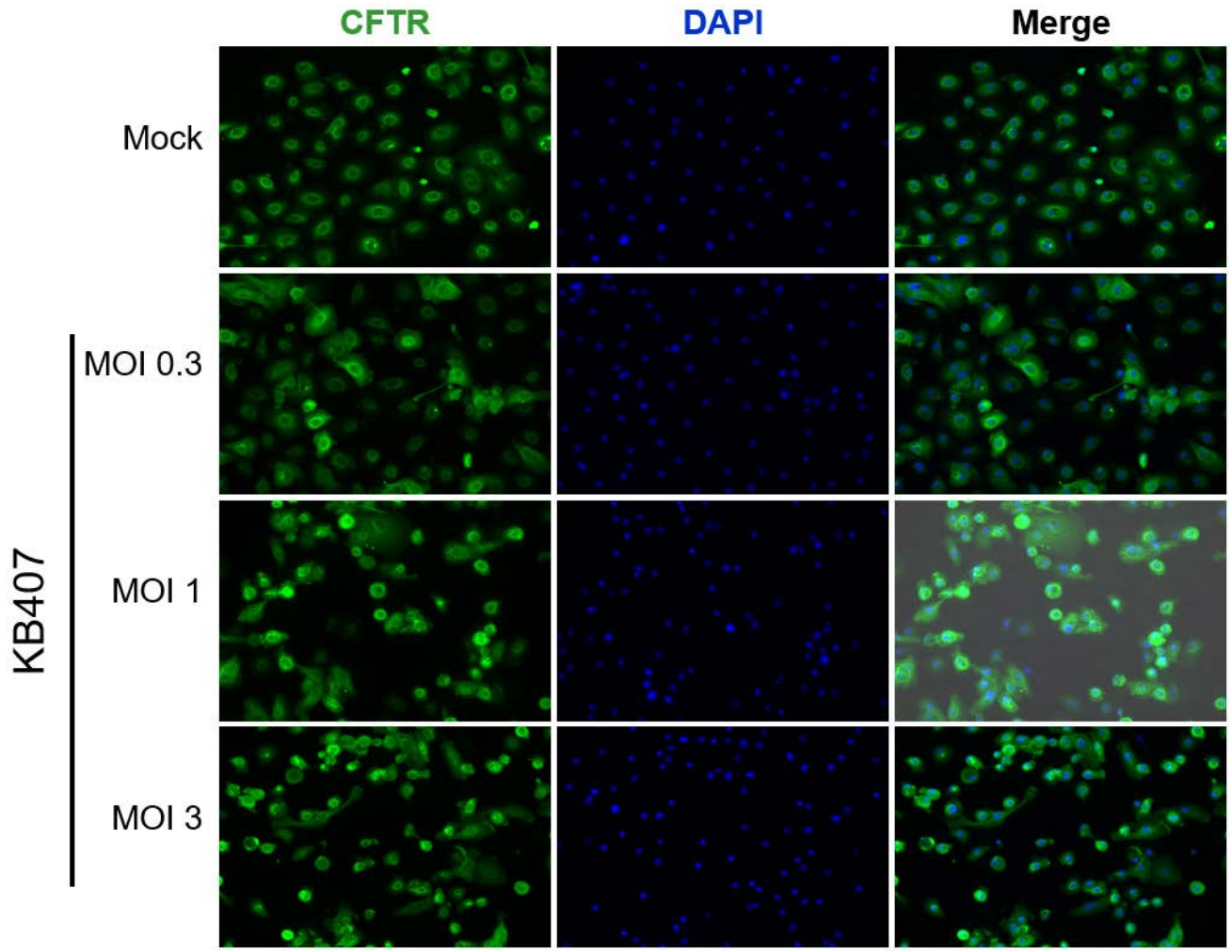
Appearance of high molecular weight doublet suggests proper maturation and trafficking of the KB407-expressed exogenous human CFTR

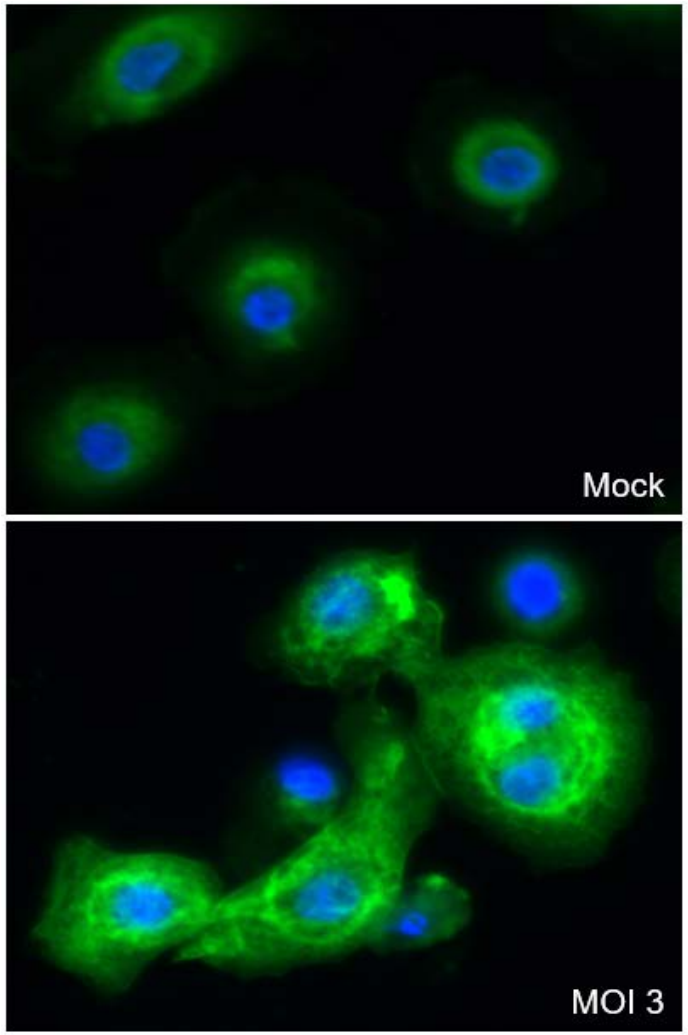


Protein activity determined using a CFTR-dependent fluorescent dye uptake assay.

KB407 in CF Patient-Derived Small Airway Epithelial Cells

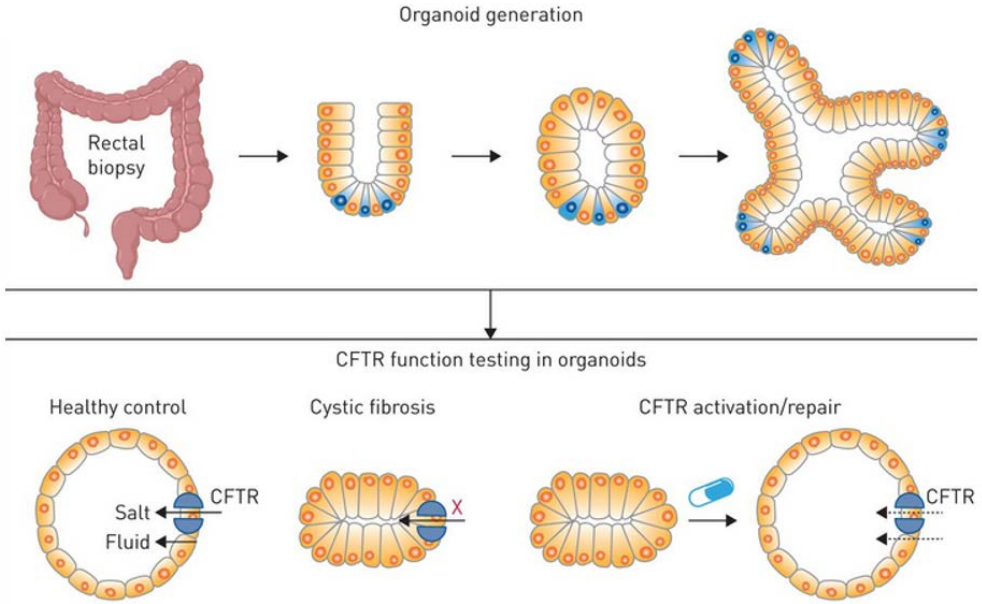
KB407-expressed human CFTR properly localizes to the plasma membrane of transduced cells



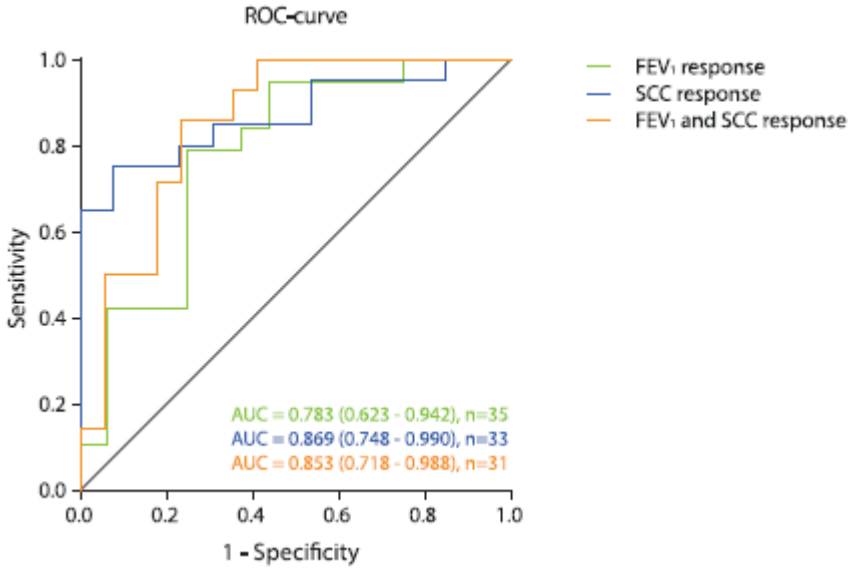


CF Patient-Derived Organoids (PDOs)

A preclinical system for predicting response to investigational therapies

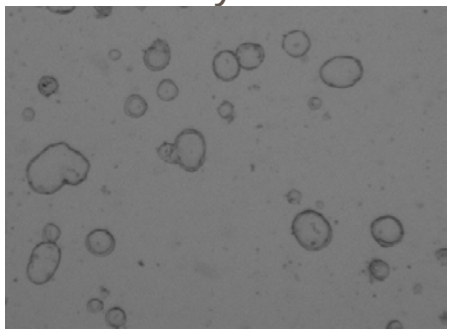


Van Mourik *et al.* (2019). "Intestinal organoids to model cystic fibrosis".

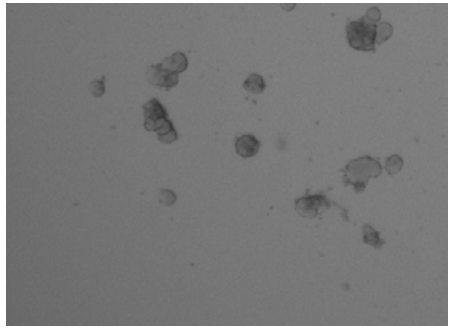


Berkers *et al.* (2019). "Rectal Organoids Enable Personalized Treatment of Cystic Fibrosis".

Healthy PDOs



CF PDOs



"Here, we provide a study that demonstrates that *in vitro* drug responses in rectal organoids from individual patients with cystic fibrosis (CF) correlate with changes in two *in vivo* therapeutic endpoints… This study indicates that an *in vitro* assay using stem cell cultures can prospectively select efficacious treatments for patients"

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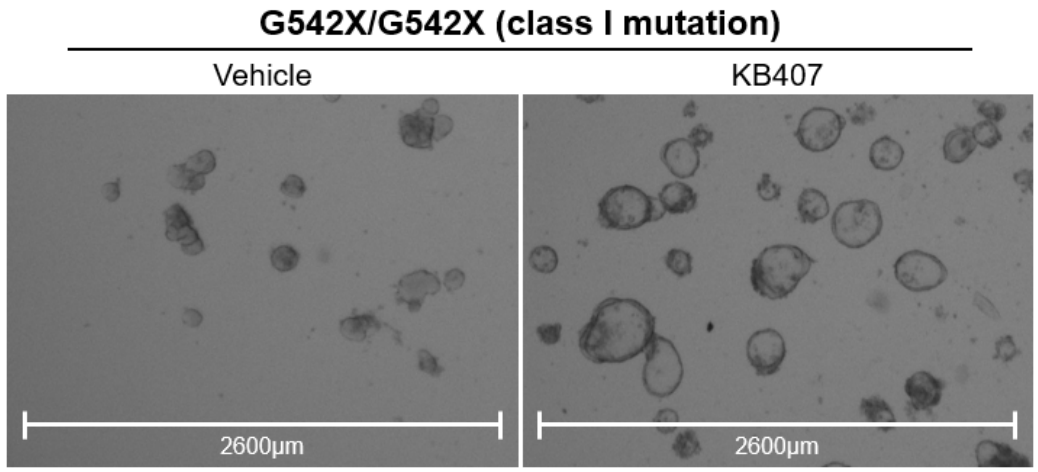
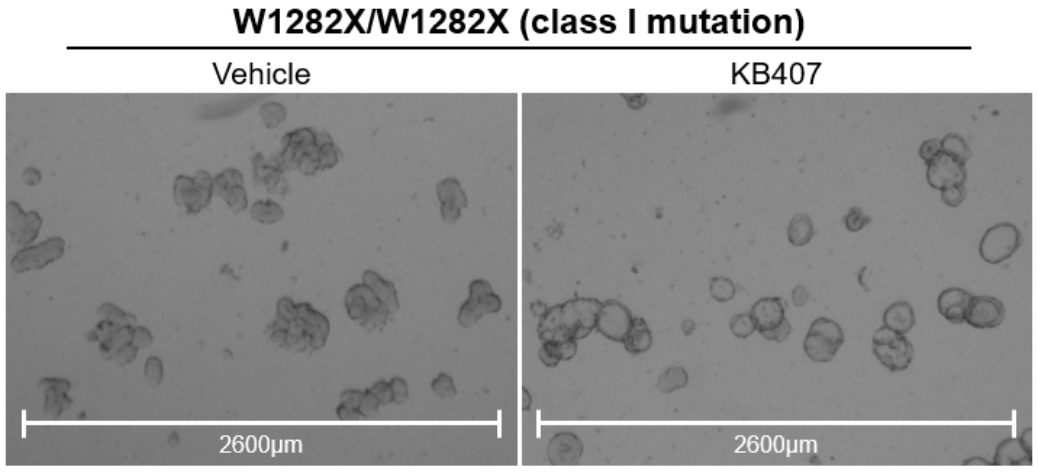
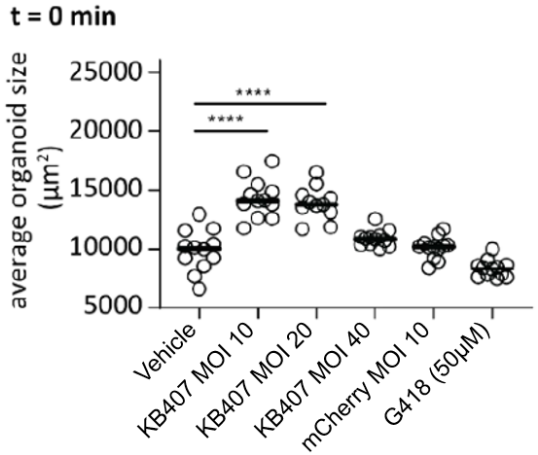
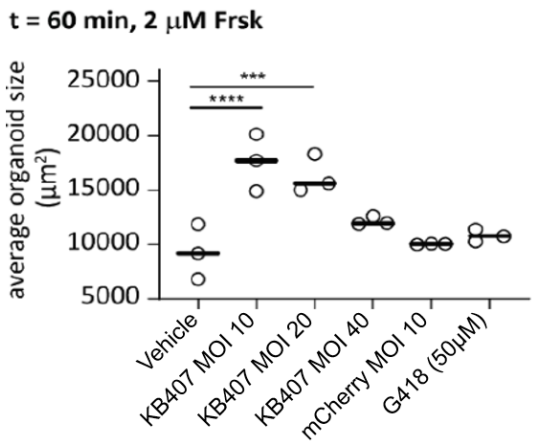
CF PDOs (Class I Mutations)

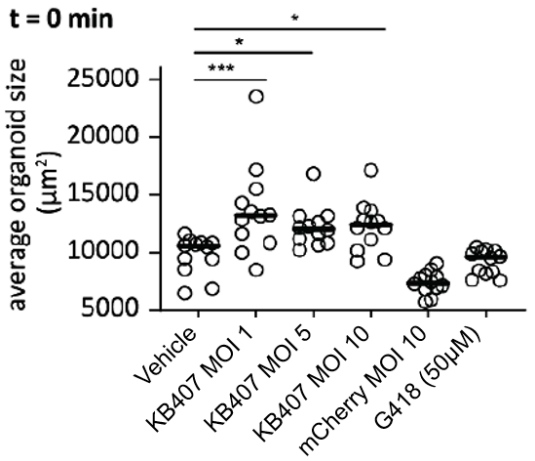
KB407-mediated functional correction of CF phenotype in clinically relevant 3D organotypic system

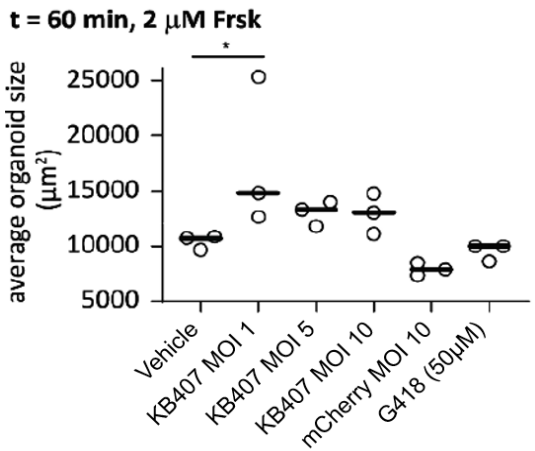












Investment Highlights and Upcoming Milestones

Investment Highlights and Upcoming Milestones

- B-VEC pivotal study to treat dystrophic epidermolysis bullosa
- Initiation of KB105 Phase 2 pediatric study
- Initiation of KB301 Phase 1 safety and efficacy study in aesthetic indication
- Initiation of Phase 1 clinical study in KB104 to treat Netherton syndrome and KB407 to treat cystic fibrosis in 1H 2021
- Cash position of ~ $300M provides runway to 2H 2022
- Inside ownership ~ 27% following recent secondary financing
- One GMP facility operational with second anticipated to be ready in 1H 2022
- Building out Global Commercial Team for anticipated launch of pipeline products in 2022

To become a fully integrated gene therapy rare disease company by 2022

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Medicines for Rare Diseases –
A Gene Therapy Company