Krystal

Medicines for Skin Diseases and Conditions –
A Gene Therapy Company

CORPORATE PRESENTATION
Q4 2019

Forward-Looking Statements

This presentation contains forward-looking statements and information. The use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify forward-looking statements. These forward-looking statements are predictions and involve risks and uncertainties such that actual results may differ materially from these statements. These risks and uncertainties include, among others: actions by the FDA and other regulatory agencies, results and timing of current and planned clinical trials, risks related to the commercialization of our products, our ability to manufacture sufficient quantities of products for clinical trials and commercial launch, and those other risks detailed from time to time under the caption “Risk Factors” and elsewhere in Krystal Biotech's Securities and Exchange Commission (SEC) filings included in our Annual Report on Form 10-K for the year ending December 31, 2018, and in future filings and reports of Krystal Biotech. The Company undertakes no duty or obligation to update any forward-looking statements as a result of new information, future events or changes in its expectations.

Company Overview

- NASDAQ: KRYS; started operations in 2016 with headquarters in Pittsburgh, Pennsylvania.
- Established a patented, fully-integrated HSV-1-based Skin TARgeted Delivery (STAR-D) gene therapy platform and a pipeline of clinical and non-clinical effectors to target rare diseases and conditions. Zero royalty burden.
- Successful completion of Gem-1 (phase I) and Gem-2 (phase II) study of KB103.
  - Received regenerative medicine advanced therapy (RMAT) designation from the FDA
  - Priority Medicines (PRIME) designation awarded by EMA
  - Pivotal study anticipated to begin in 1H 2020
- Investigational New Drug (IND) application for KB105 submitted to FDA
  - Two patients dosed in GEM-3 study to-date; interim results announcement anticipated in 1H 2020
- Filing INDs for KB104 (Netherton Syndrome) and KB301 (undisclosed aesthetic condition) expected in 1H 2020.
- US Patents 9,877,990 (KB103; issued 1/16/18), 10,155,016 (KB103; issued 12/18/18), 10,441,614 (STAR-D platform; issued 10/15/19) covering pharmaceutical compositions and methods of their use.
- First GMP in-house manufacturing facility in Pittsburgh, PA complete. Breaking ground on second GMP facility anticipated in Q4 2019.
- Insider ownership (management, employees, directors): 28% of fully diluted shares outstanding (as of 9/30/19)

Fully-Integrated STAR-D Gene Therapy Platform

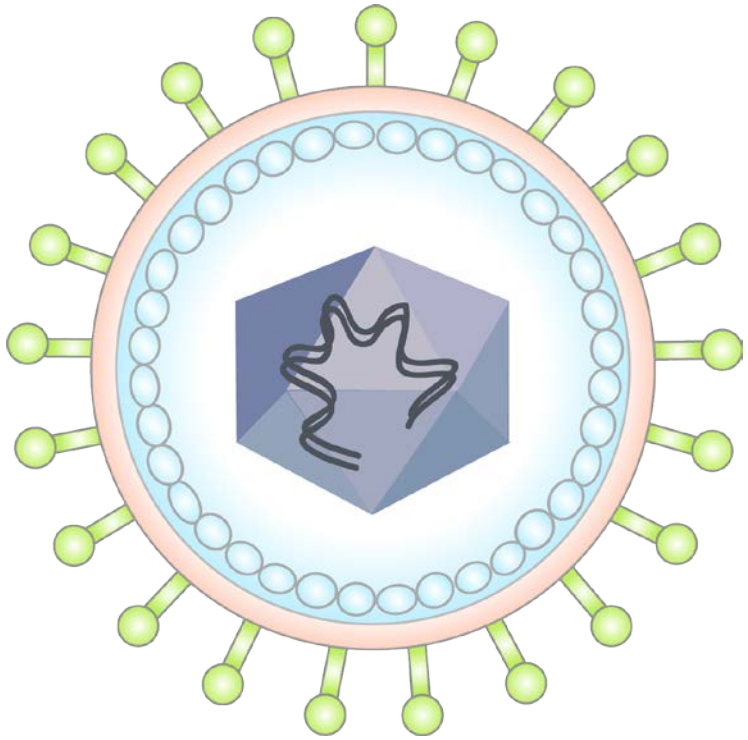
Modified Herpes Simplex Virus 1 (HSV-1) vector well suited to treat skin diseases

Proprietary Vectors
and underlying cell lines support robust and flexible drug production

Direct delivery
Topical administration for open wounds and intradermal for intact skin

Reproducible and Scalable Manufacturing
using internally developed and validated protocols

Non-integrating
into the DNA making it safer



Significant payload capacity
due to ~150Kb genome to accommodate multiple genes and effectors in the backbone

Stability
of vector beneficial to production and storage

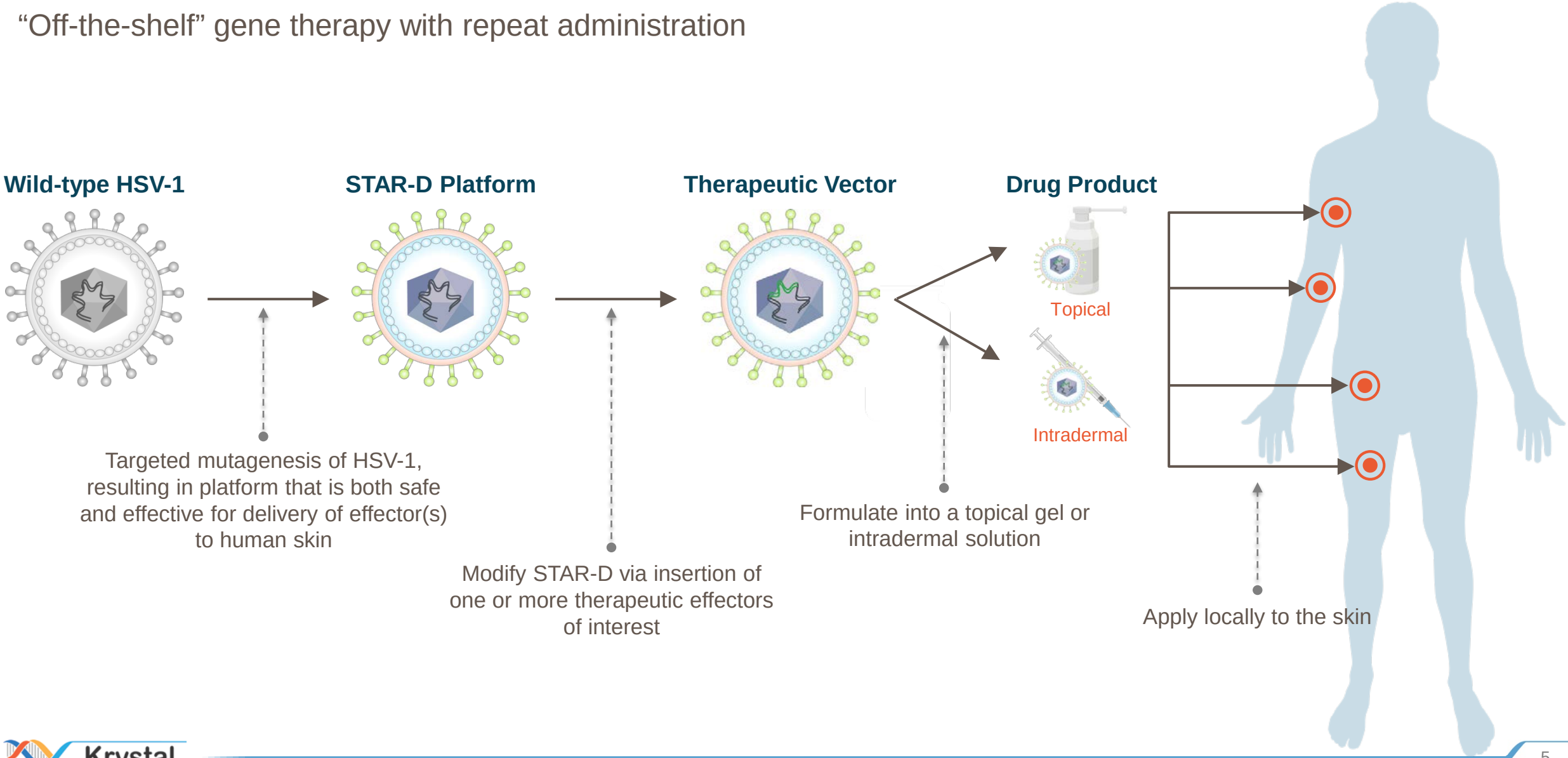
High Transduction Efficiency
Transduces dividing and non-dividing skin cells

Non-Replicating
Safe for repeat administration; transient transgene expression, diluted by cell divisions

Regulatory precedent
HSV-1 used as backbone in Amgen's Imlygic®, which is approved for melanoma and administered weekly to patients

Krystal's Unique and Straightforward Approach

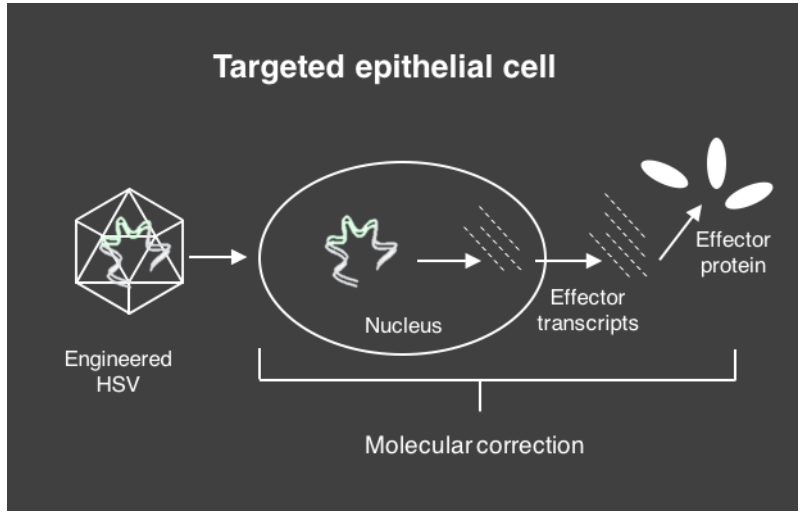
"Off-the-shelf" gene therapy with repeat administration



Krystal's Approach: Applicable to a Wide Range of Skin Diseases and Conditions

1. Severe monogenic skin diseases

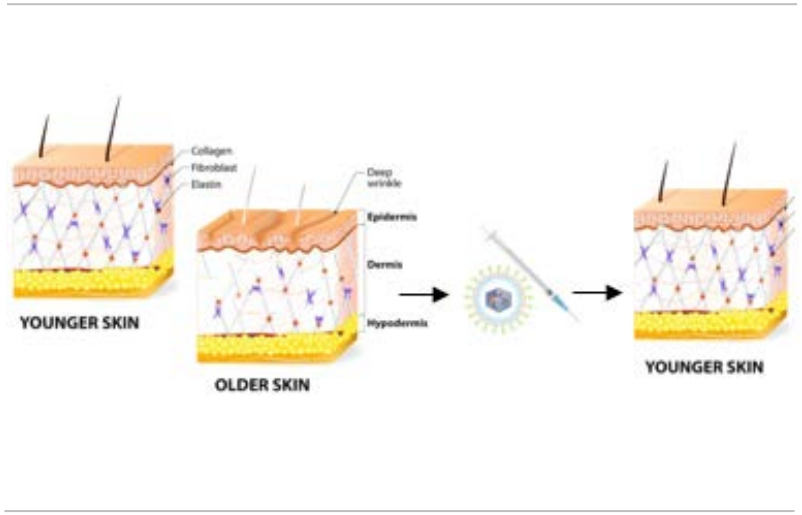
Indications: Dystrophic Epidermolysis Bullosa (DEB); Autosomal Recessive Congenital Ichthyosis (ARCI); Junctional Epidermolysis Bullosa (JEB); Netherton Syndrome (NS)



Effectors: *COL7A1* (type VII collagen); *TGM1* (transglutaminase-1); laminins; *SPINK5* (serine protease inhibitor kazal-type 5)

2. Aesthetic conditions

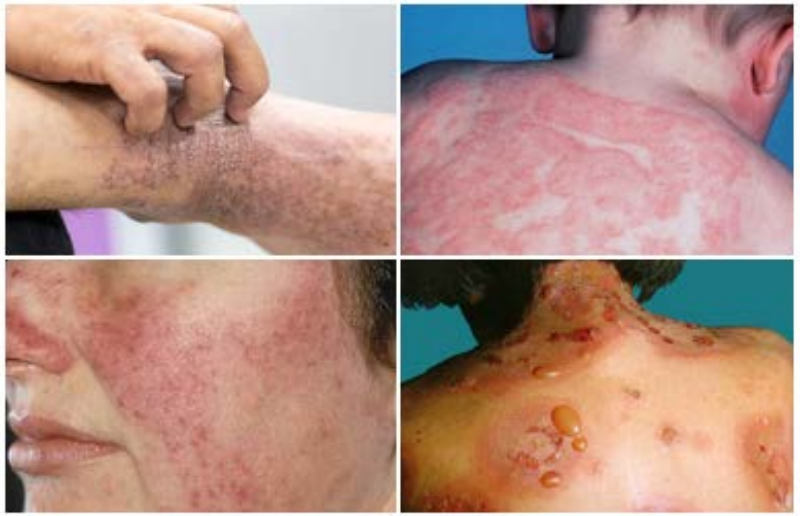
Indications: fine lines; nasolabial folds; glabellar lines; depressed scars; UV-induced skin damage



Effectors: Collagens

3. Chronic skin diseases

Indications: atopic dermatitis; psoriasis; rosacea; acne



Effectors: Anti-inflammatory antibodies and antibody fragments

Krystal's Current Pipeline

Product	Indication	Discovery	Preclinical	Phase I/II	Phase III	Marketed
KB103†¤•Δ‡§	**Dystrophic EB**					
KB105†¤•‡	**TGM1-deficient ARCI**					
KB301 / KB302	**Aesthetic Skin Conditions**			IND to be filed 1H 2020		
KB104	**Netherton Syndrome**			IND to be filed 1H 2020		
KB5XX	**Chronic Skin Diseases**					

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

KB103*

USAN: *bercolagene telserpavec*

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)

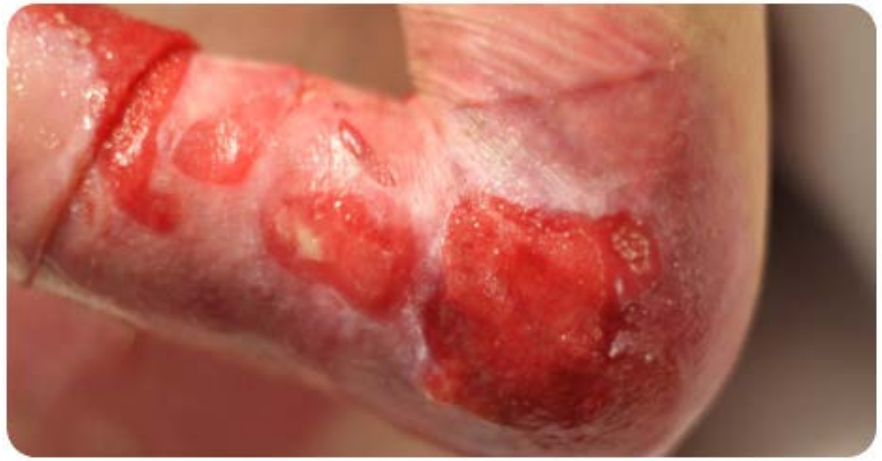
"Butterfly Children" is used to describe young DEB patients because their skin is as fragile as a butterfly's wings

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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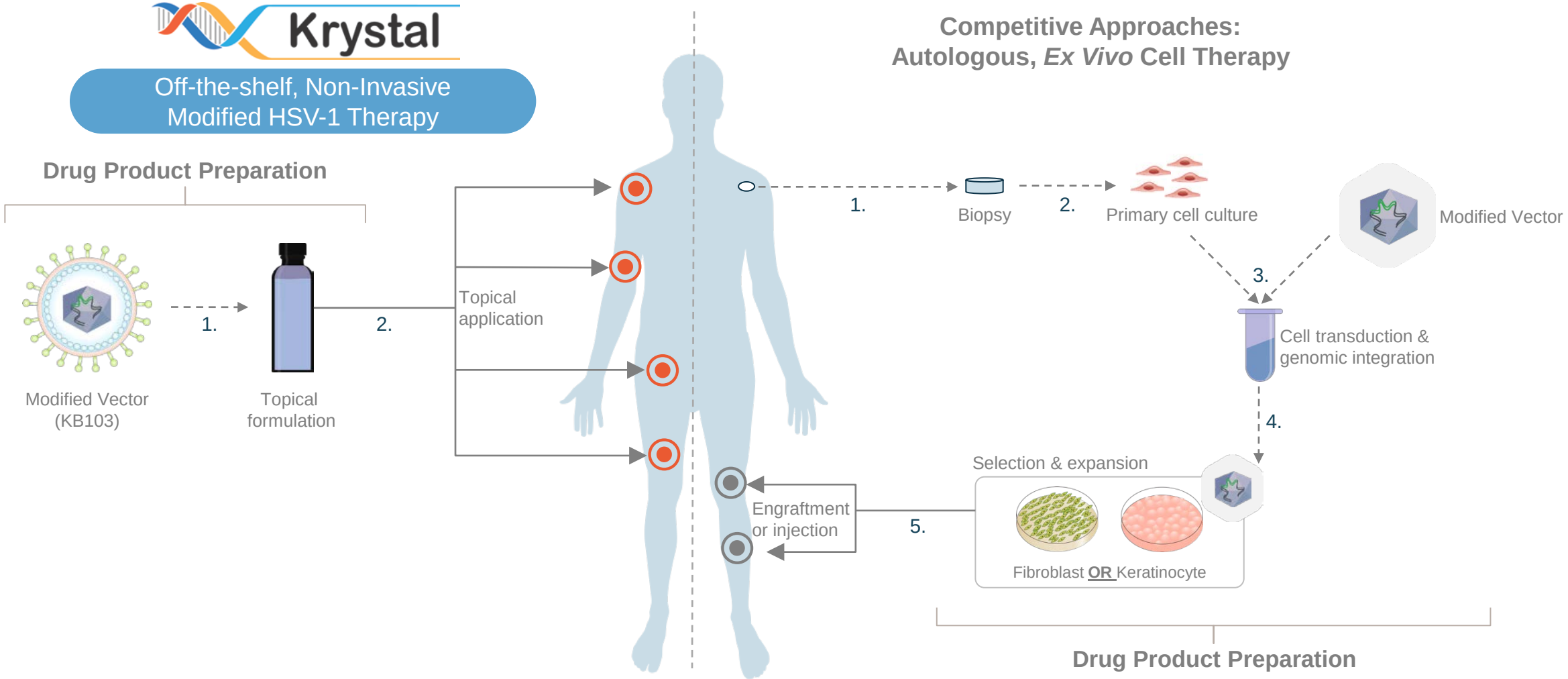
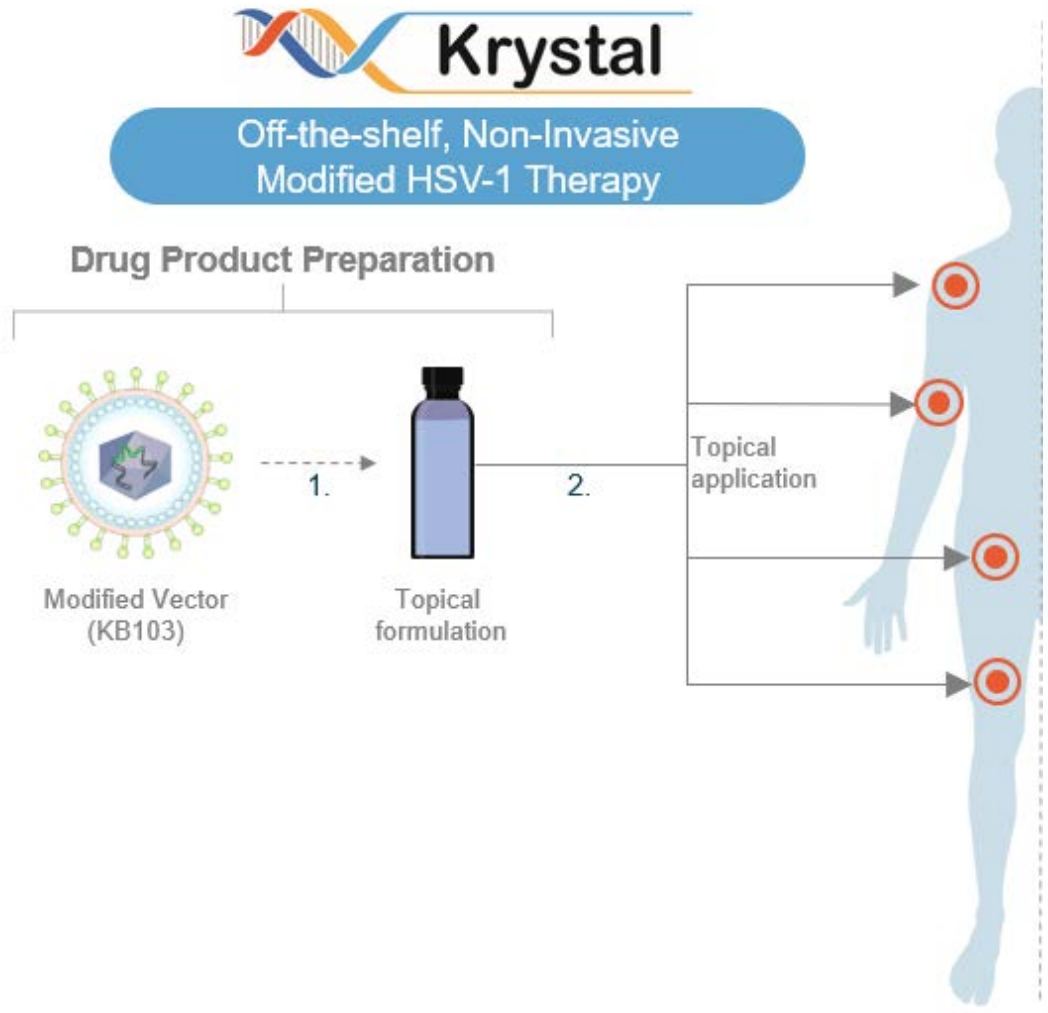
Off-the-shelf, Non-Invasive
Modified HSV-1 Therapy



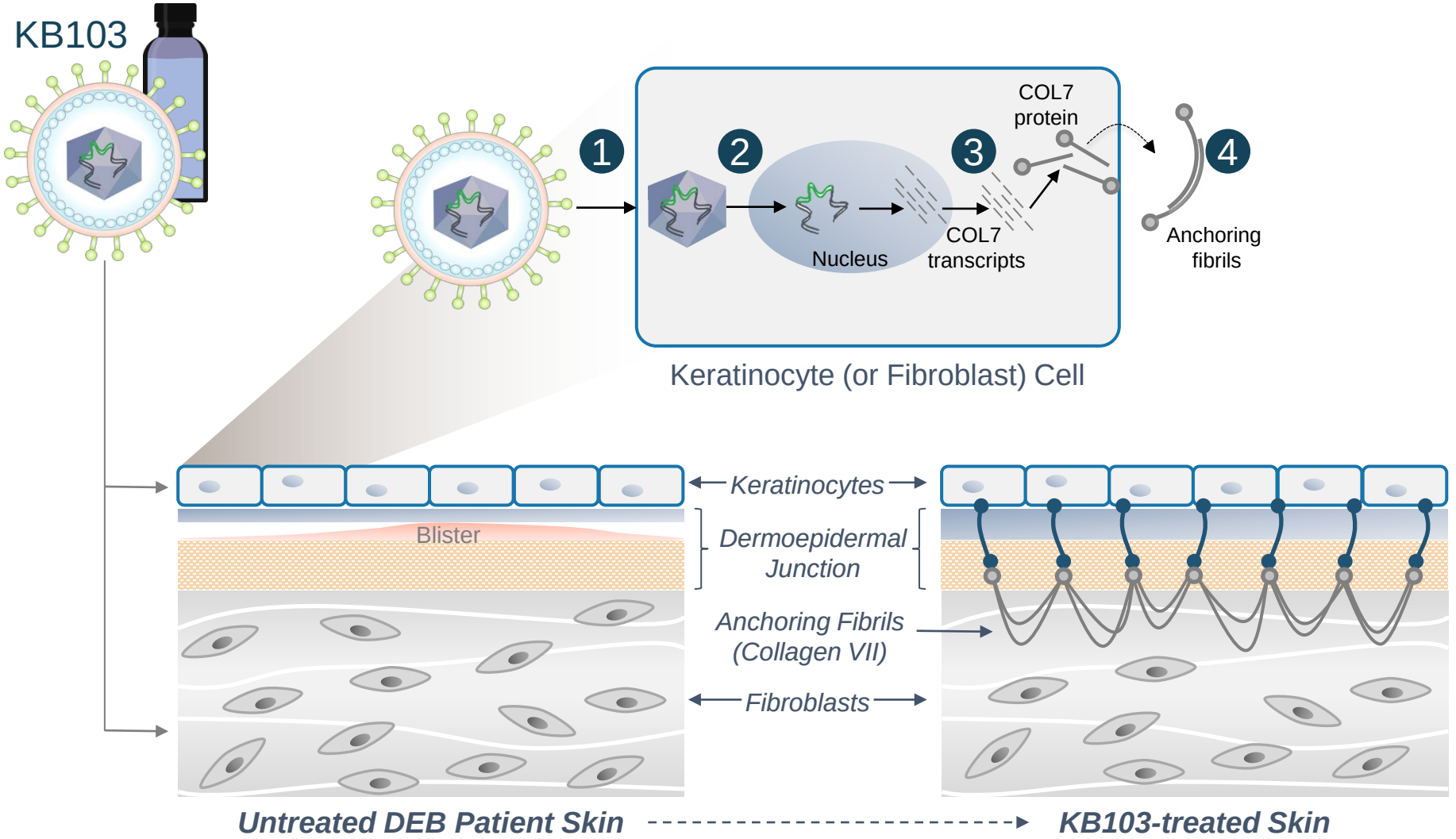
Simple, Painless and Easy to Administer



Benefits of Krystal's approach:

- Drug product ready for use in multiple patients
- Manufacturing and supply chain costs are lower
- Therapy can be administered by any care giver
- Outpatient; no hospitalization needed
- Does not require expensive, invasive, and time-consuming procedures or sophisticated medical teams
- Taking gene therapy to the patient
  - Minimizes patient travel and circumvents upfront burdens typical of gene therapies

KB103 Mechanism of Action



1. KB103 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

KB103 Status

- Interim phase I data announced (2 patients total)
- Four patients dosed in Phase II study

- Announced phase I/II data (6 patients total)
- Two additional patients dosed in Phase II study

- Announced phase I/II data update (8 patients total)

- Initiate pivotal trial

- Initiate clinical study in EU
- Anticipate filing of KB103 biologics license application (BLA)

KB103 Clinical Data

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GEM-1: Phase I Trial Design

A phase I study of KB103, a non-integrating, replication-incompetent HSV vector expressing the human collagen VII protein, for the treatment of dystrophic epidermolysis bullosa (DEB)

- Key objectives: Demonstrate efficacy and safety of KB103
- Primary Objectives: Expression of COL7, presence of anchoring fibrils, and safety
- Secondary Objectives: Change in wound area, duration of wound closure, time to wound closure
- Principal investigator: Dr. Peter Marinkovich, MD, Dermatologist, Stanford University
- Trial Design:
  - Randomized, open-label, placebo controlled
  - 2 wounds treated topically: 1 placebo, 1 active
  - 1 intact site treated intradermally
  - Patients were evaluated for COL7 expression by immunofluorescence and for the presence of anchoring fibrils by electron microscopy
  - Initial dosing at Day 0 and a repeat dose a month later; Patient 02 was additionally dosed on Day 14 and Day 42 by PI to understand impact of incremental dose escalation

GEM-2: Phase II Trial Design

Four patients enrolled in December 2018. Principal Investigator: Dr. Peter Marinkovich, Stanford University

Key objectives: Demonstrate safety and wound healing of KB103

- **Primary Clinical Objectives**: Safety and Wound healing (time to wound closure, % area of wound closure, duration of wound closure)
- **Secondary Mechanistic Objectives**: Expression of COL7, evidence of anchoring fibrils.

Trial Design:

- Randomized, placebo-controlled study
- 3 wounds treated topically in each patient: 1 placebo, 2 active
- Initial front-loaded dosing for 5 days (3e8 pfu/day)
- Biopsies were based on PI discretion during site visits.
- Biopsied wounds were dosed one administration of 3e8 at site of biopsy, following a biopsy
- Each patient is on-study for approximately six months; three months of on-site visits followed by a 3-month at-home imaging period

GEM-2: KB103 Phase I and Phase II Safety Update in Wounds

KB103 continues to be well tolerated following initial and repeated dose

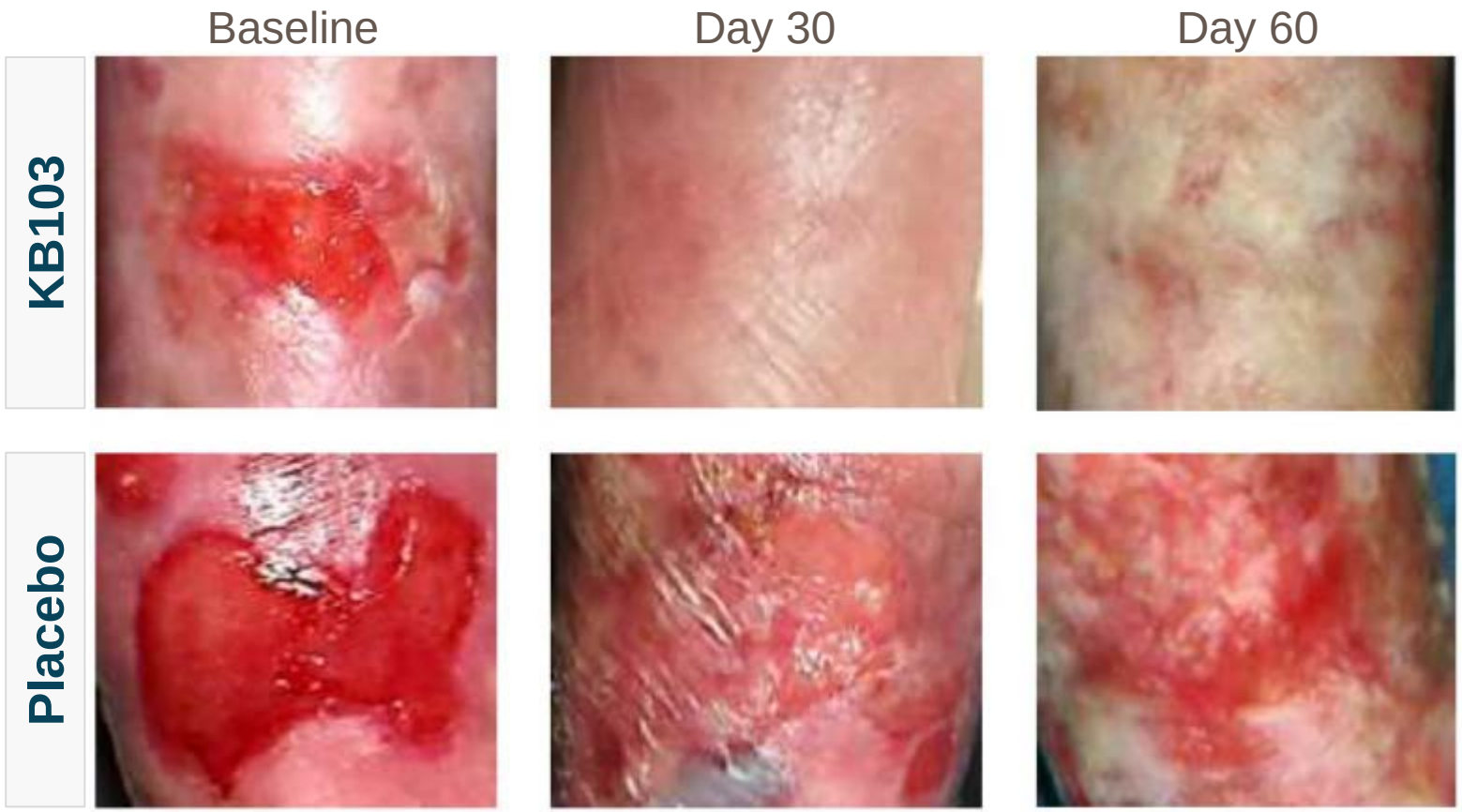
- No treatment-related adverse events (serious or otherwise) were reported.
- No immune response or blistering observed around the sites of administration following first and repeat doses.
- Blood and urine samples collected throughout the study revealed:
  - No viral shedding
  - No adverse events associated with routine labs (chemistry and hematology)
  - No antibodies to COL7 were detected

Combined Summary Efficacy Update

- 9 out of 10 wounds closed completely (100% closure) following initial administrations of KB103.
- The average time to 100% wound closure on the 9 KB103 treated wounds was 17.4 days (median 14 days).
- The average duration of wound closure on the 9 KB103 treated wounds at last measured timepoint was 113 days (median 110 days).
- The wound that did not close was re-administered KB103 and closed completely within 7 days following re-administration.
  - The wound was originally reported to be open for over 4 years.
  - The wound has remained closed for over 100 days (and ongoing).

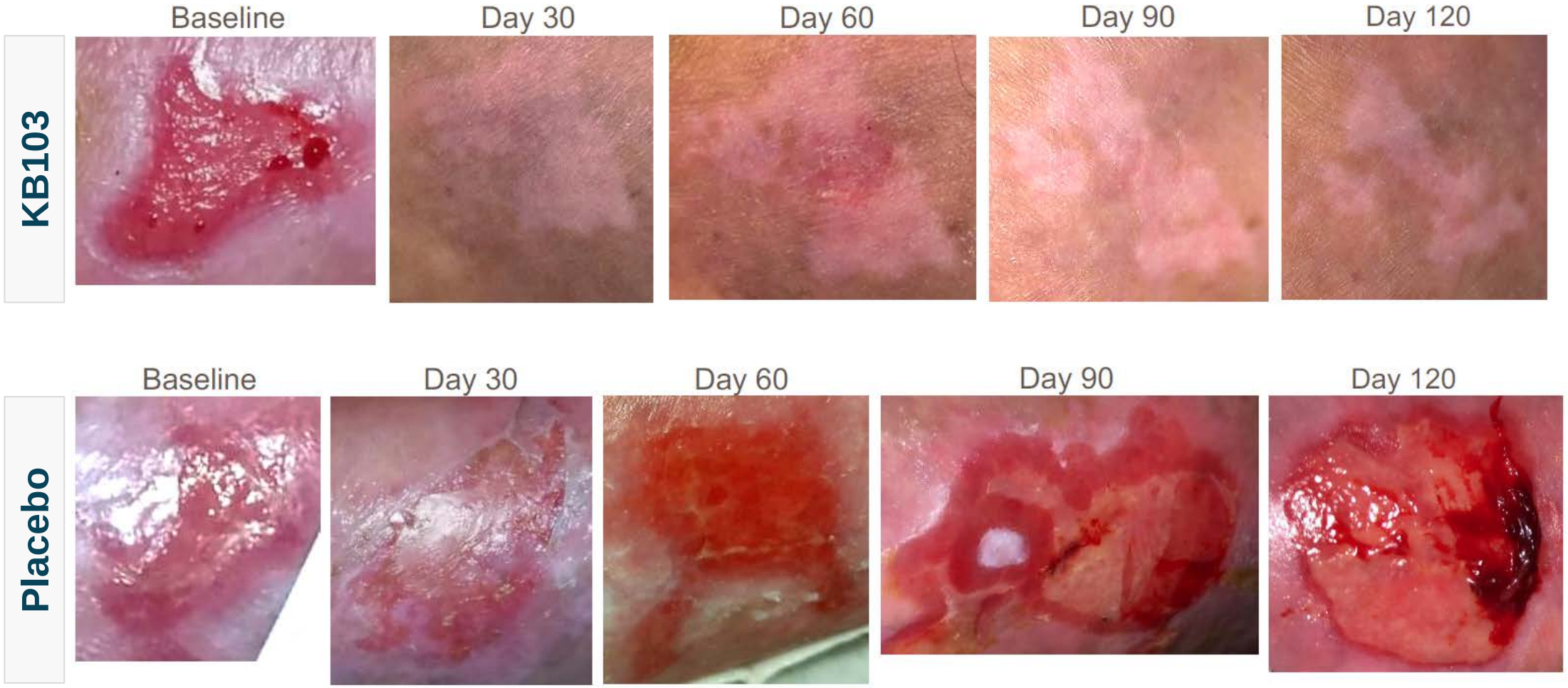
Phase I Study: Illustrative Wound Healing Data

Patient 02, KB103- and placebo-randomized wounds



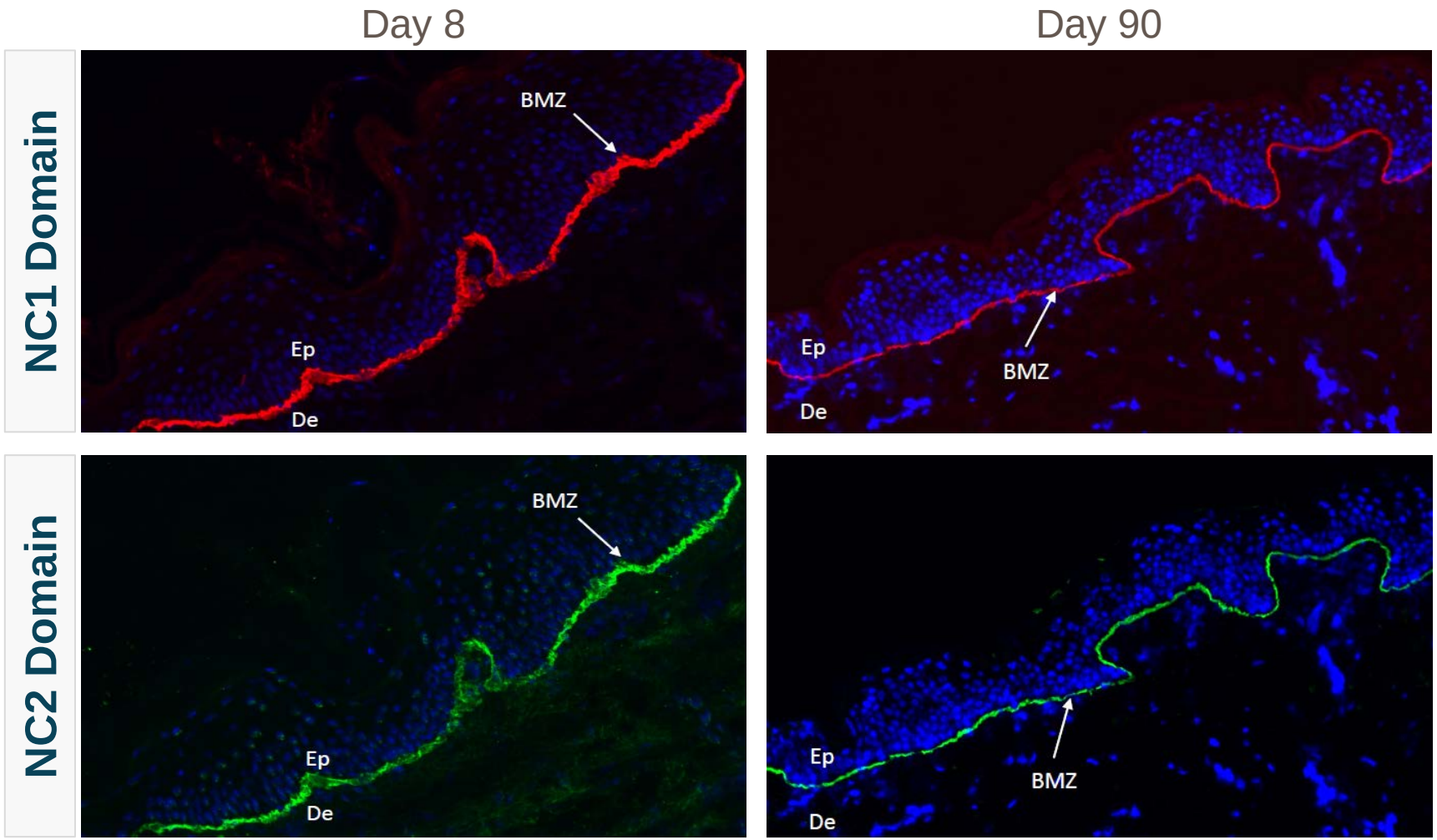
Phase II Study: Illustrative Wound Healing Data

Patient 05, KB103- and placebo-randomized wounds



Phase II Study: Illustrative Mechanistic Data

Patient 06, Collagen VII staining by immunofluorescence in KB103-treated skin

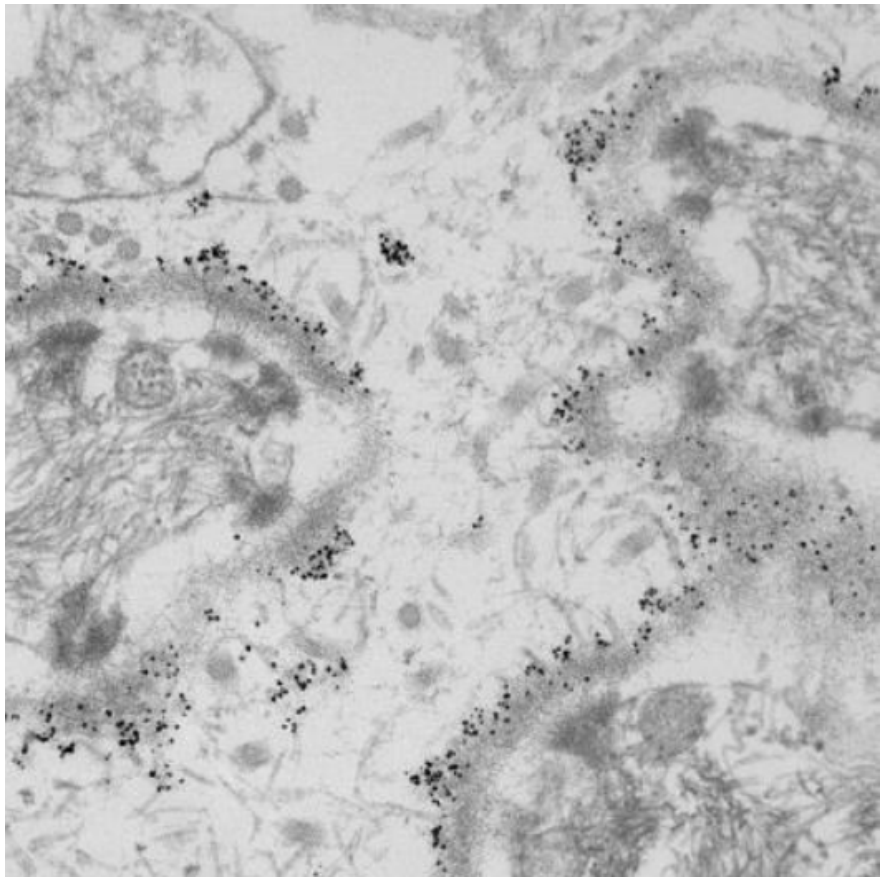


Ep: epidermis; De: dermis; BMZ: basement membrane zone

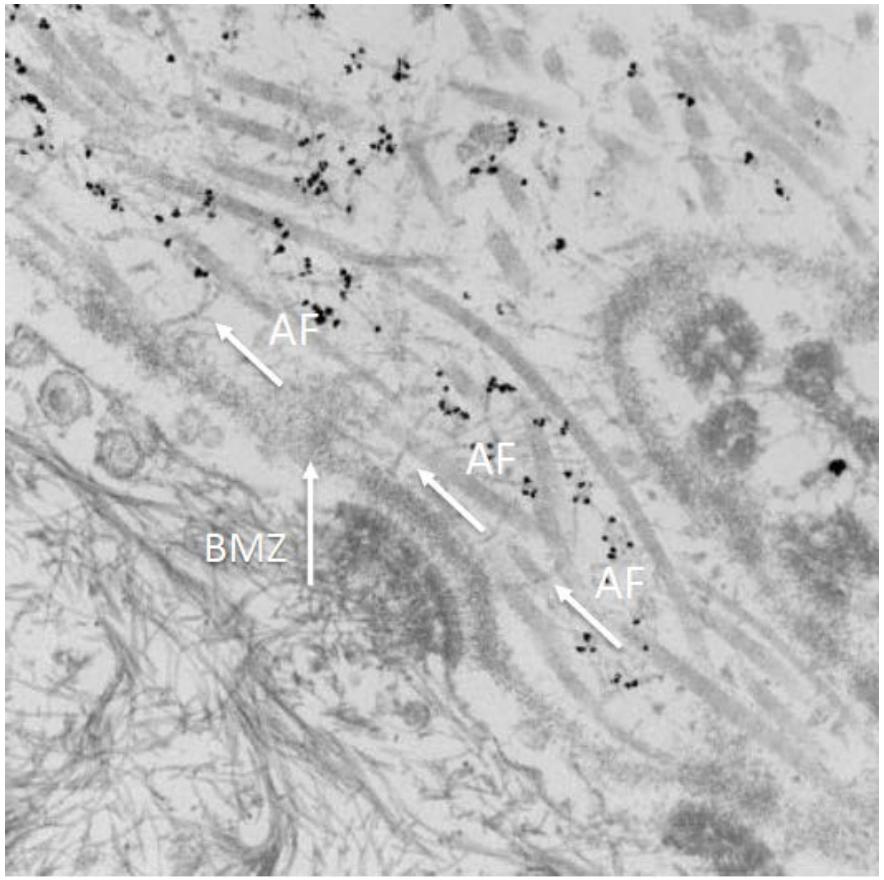
Phase II Study: Illustrative Mechanistic Data

Patient 06, anchoring fibril staining by immunoelectron microscopy in KB103-treated skin

NC1 Domain



NC2 Domain



AF: anchoring fibrils; BMZ: basement membrane zone

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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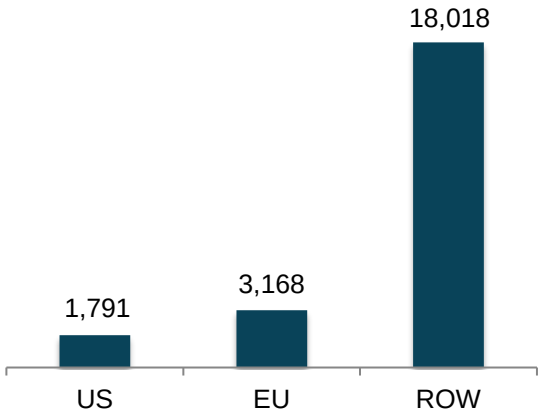
ARCI Associated With TGM1

Autosomal Recessive Congenital Ichthyosis (ARCI) associated with TGM1

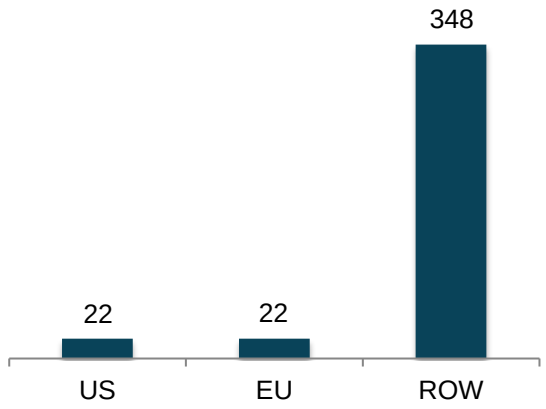
A condition characterized by thick dry scaly skin, increased trans-epidermal water loss (TEWL), risk for dehydration, sepsis, skin malignancies, *etc*.

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

Prevalence[1-8]



New Cases/Year



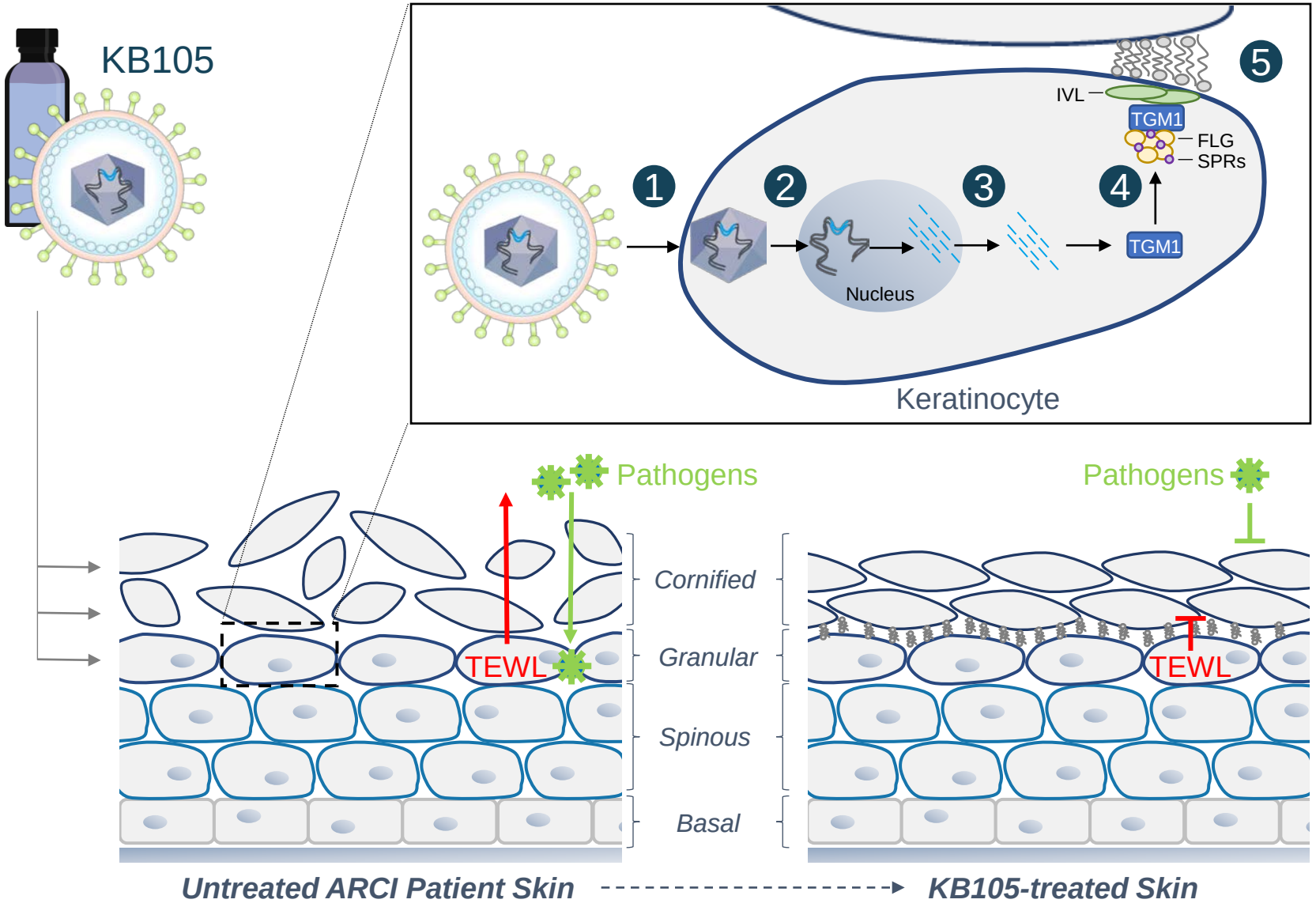
Current Standard of Care

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).

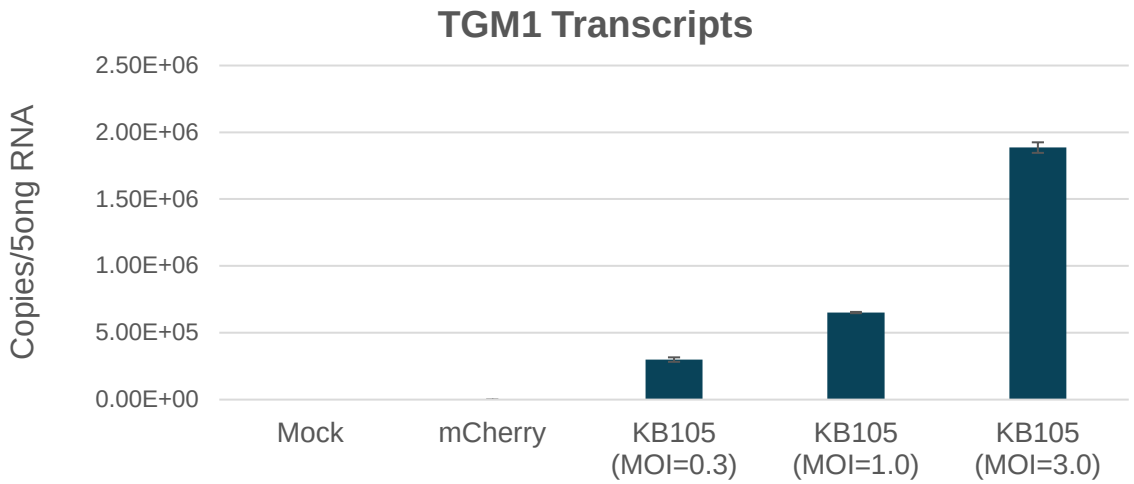
KB105 Mechanism of Action

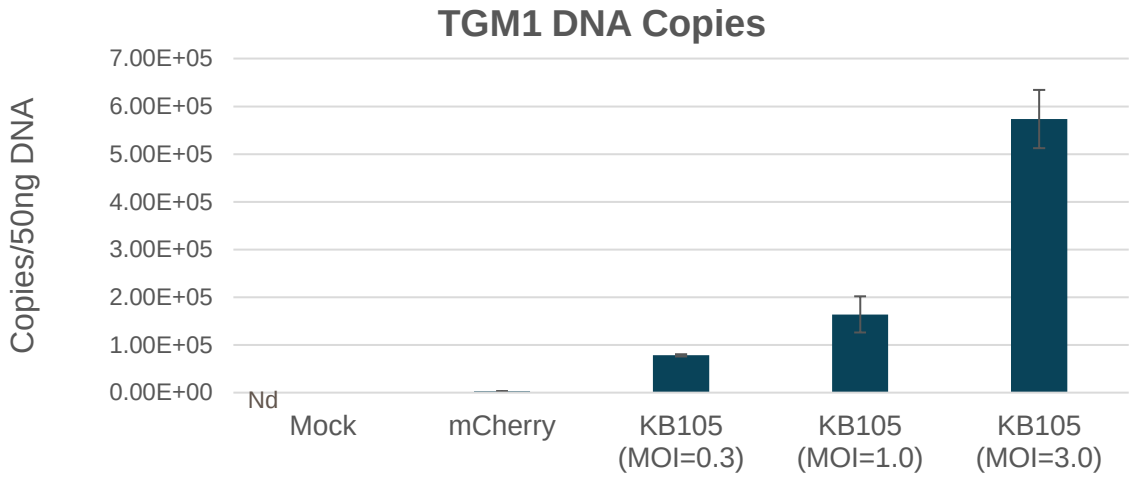


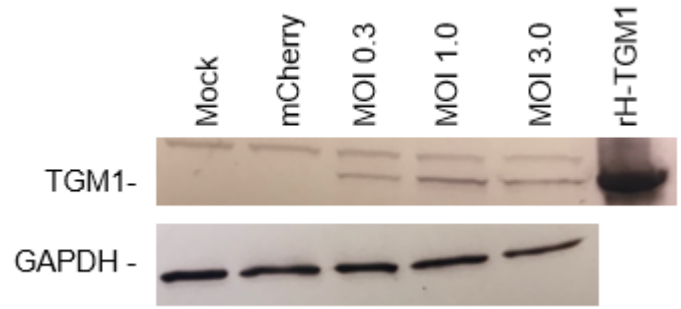
1. KB105 enters permeabilized skin and transduces keratinocytes (native TGM1-producing cells)
2. KB105 is transported into the nucleus of transduced cells and the vector genome is deposited (episomally)
3. *TGM1* transcripts are generated, which allows the cell to produce functional TGM1 protein that 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

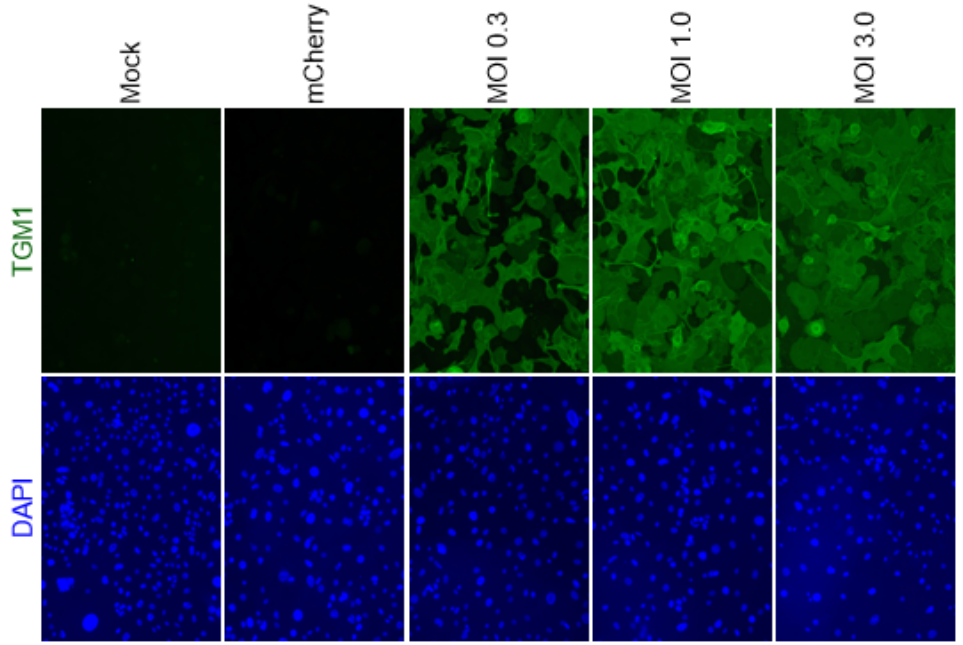
KB105 Preclinical: Immortalized TGM1-Deficient ARCI Keratinocytes

Robust TGM1 expression detected at the transcript and protein levels, with no obvious dose-dependent toxicity



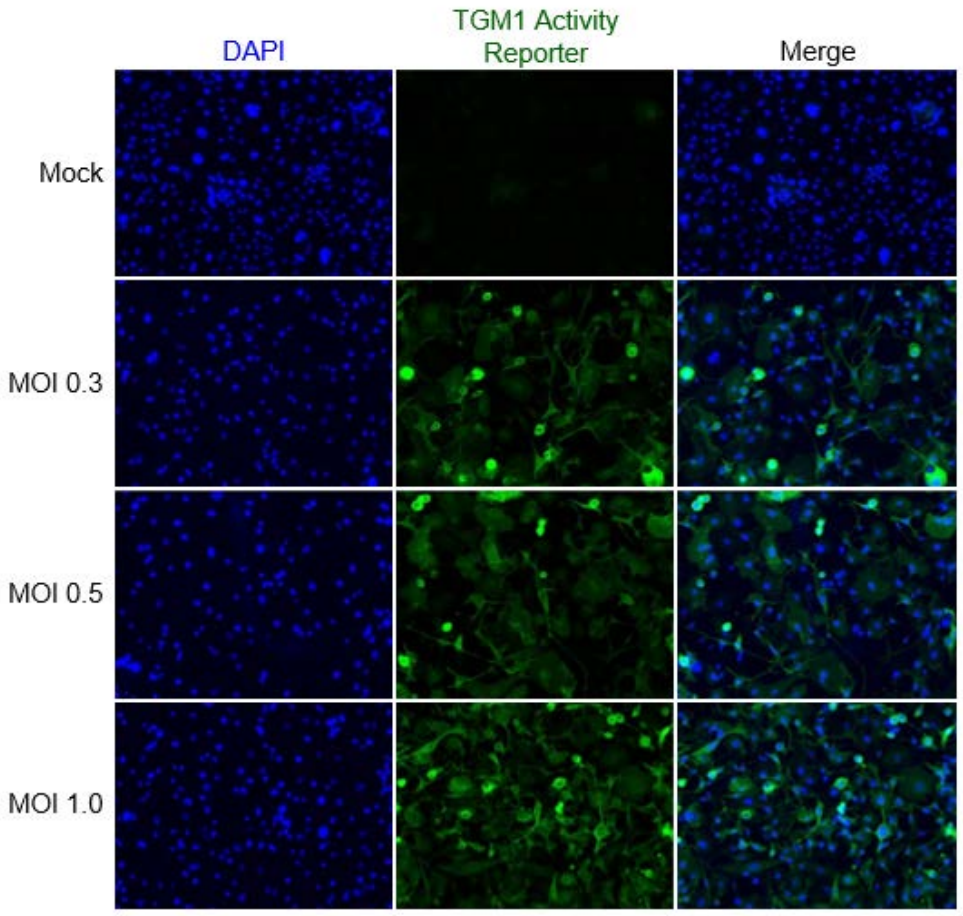


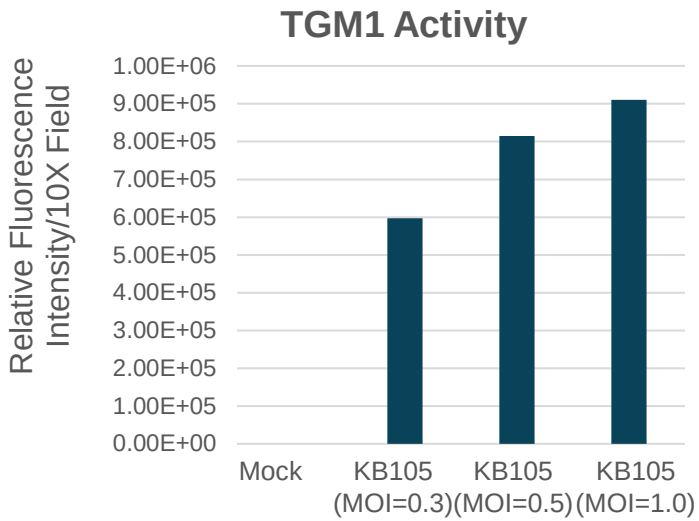


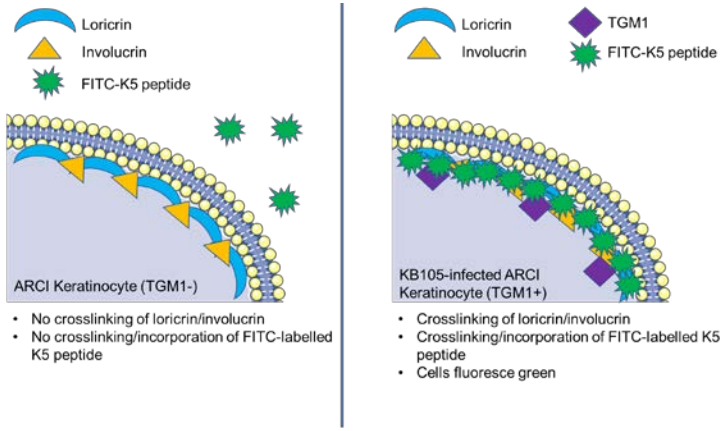


KB105 Preclinical: TGM1 Function

Dose-dependent increase in functional TGM1 detected in KB105 infected primary TGM1-deficient ARCI keratinocytes



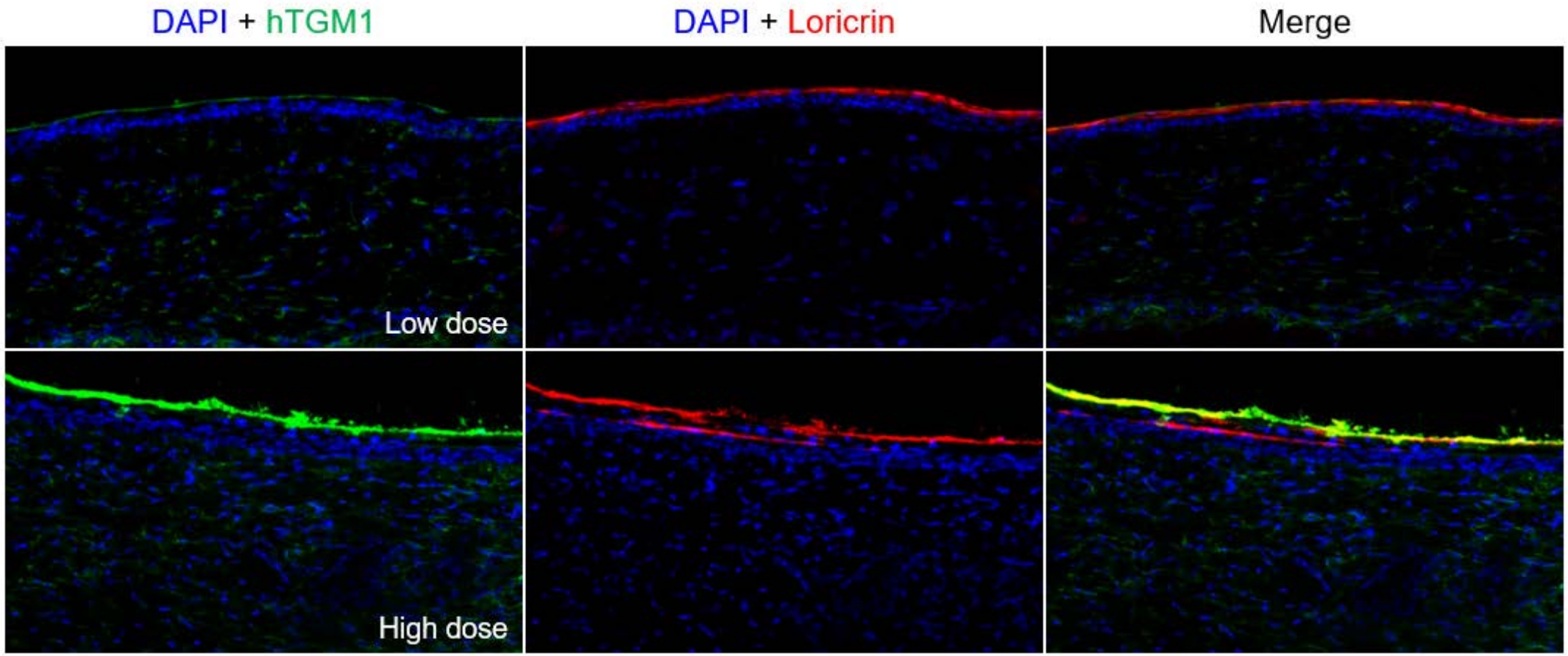




TGM1 activity determined using a fluorescent synthetic peptide reporter assay measuring TGM1-mediated glutamine conjugation

KB105 Preclinical: *In Vivo* Single Topical Administration

Properly localized dose-dependent human TGM1 detected 48 hours after topical KB105 application in mice



Loricrin is both a substrate for TGM1 and serves as a marker for the stratum granulosum/spinosum - indicates that TGM1 colocalizes with at least one native substrate and is expressed in the correct layer of skin

KB105 Preclinical: GLP Repeat Dose Toxicity and Biodistribution in Mice

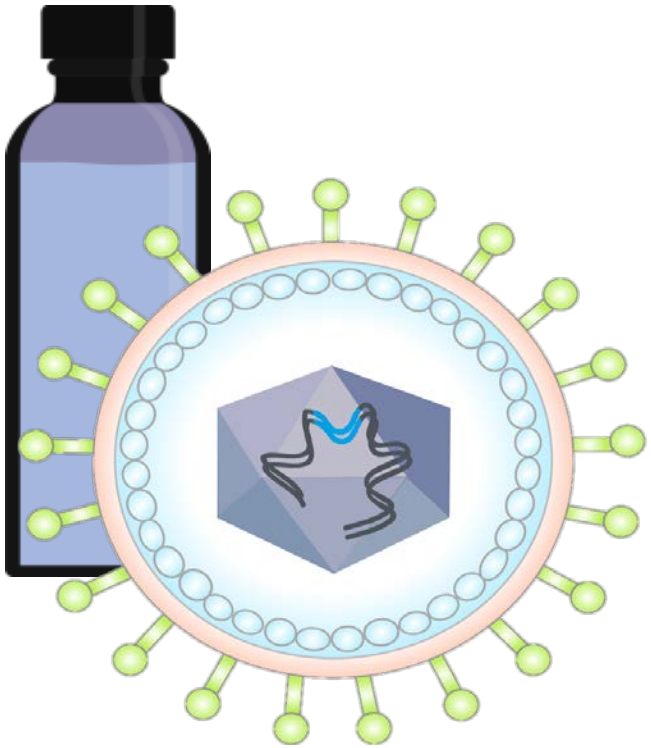
Repeated application of high dose topical KB105 was well tolerated and localized

Five weekly administrations of 1.07 x 10^9 pfu/day KB105 via topical application to the dorsal skin of male and female mice were well tolerated.

- NOAEL dose: 1.07 x 10^9 pfu/day
- No KB105-related mortality, clinical observations, body weight or food consumption changes, macroscopic findings, or effects on organ weight parameters were noted.
- All animals survived until their scheduled necropsy.
- Minor increase in incidence of edema at the dose site in males between Days 16 and 30 of the dosing phase and persistence of erythema at the dose site during the recovery phase in females were not considered adverse based on severity.
- High copy levels of KB105 detected at (and limited to) the dose site of all KB105-treated animals
  - On Day 3, 3.6x10^7copies/ug tissue
  - On Day 30 1.3x10^7 copies tissue – demonstrates successful repeat dosing

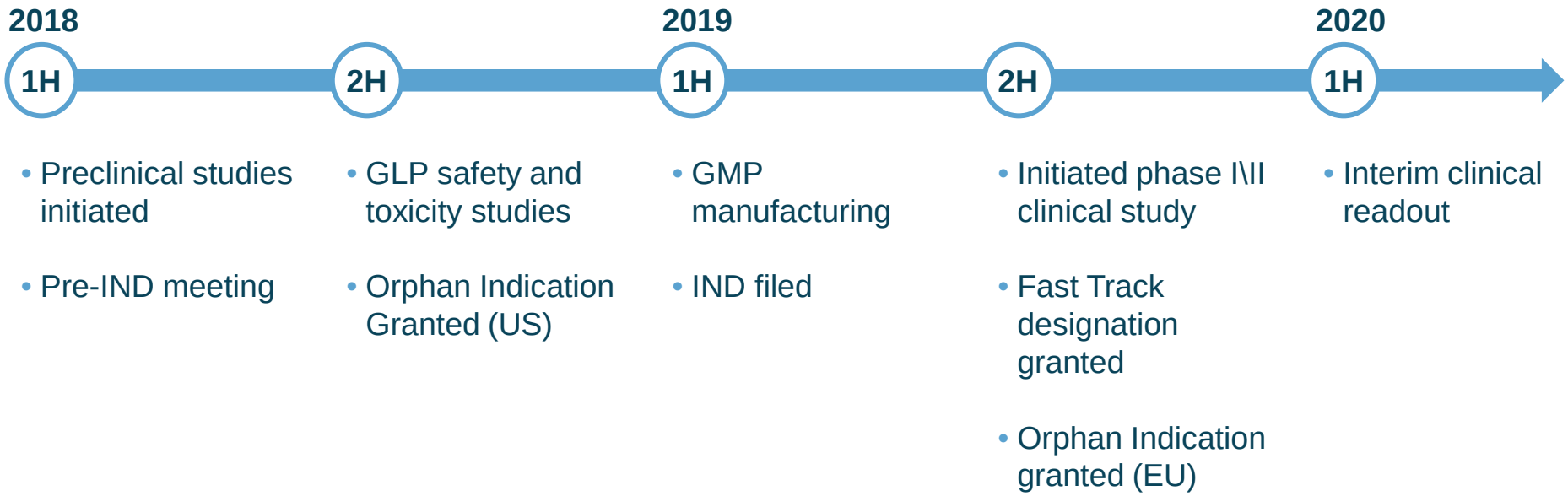
KB105 Conclusions

- *In vitro* and *in vivo* proof-of-concept and safety established for KB105
  - KB105 efficiently transduces patient keratinocytes to express functional human TGM1.
  - Topical KB105 efficiently transduces permeabilized skin and expresses human TGM1 *in vivo* in mice, in a dose-dependent manner.
  - KB105-expressed TGM1 colocalizes with native TGM1 substrates, indicating delivery to the appropriate epidermal layer.
  - Biodistribution and toxicity data indicate that KB105 can be safely and repeatedly administered to the skin at high doses without systemic vector exposure.
- KB105's robust production of TGM1 *in vitro* and *in vivo* supports its use in ARCI patients



KB105 Timeline to Clinical Readout

Phase I/II clinical trial initiated September 2019



KB104

For the treatment of Netherton Syndrome

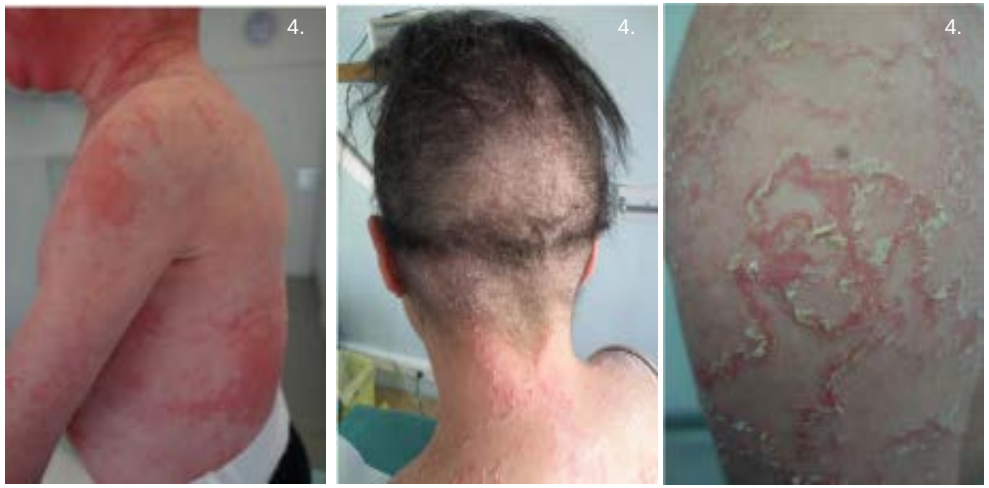
Krystal

Netherton Syndrome (NS)

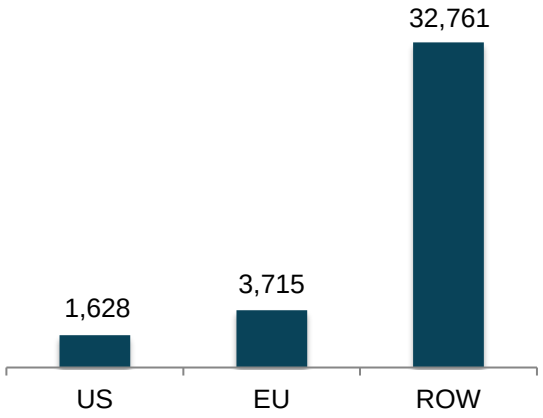
Netherton Syndrome

A life-threatening condition characterized by red, inflammatory scaling on the face, shoulders, and back, as well as short, brittle, and broken “bamboo hair”.

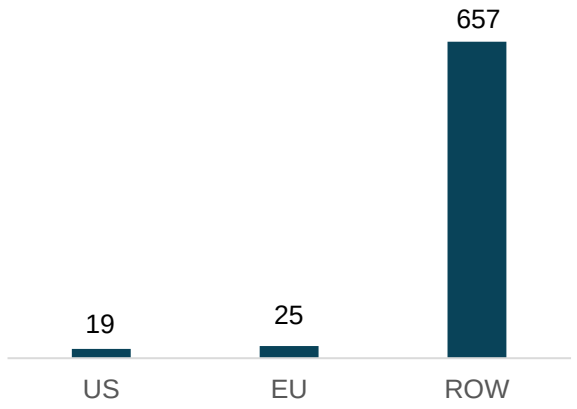
Caused by loss-of-function mutations in the *SPINK5* gene that is otherwise required for maintaining integrity and protective barrier function of the skin by regulating desquamation-involved proteases



Prevalence[1]



New Cases/Year[2,3]



Current Standard of Care

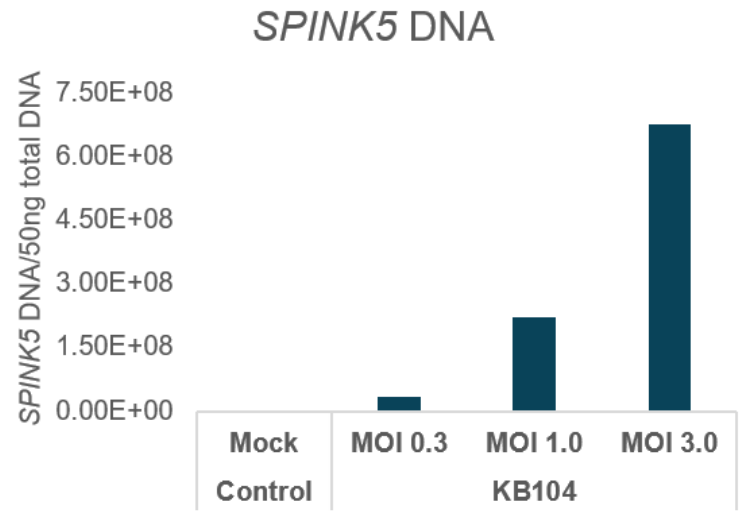
There are no approved treatments for Netherton Syndrome

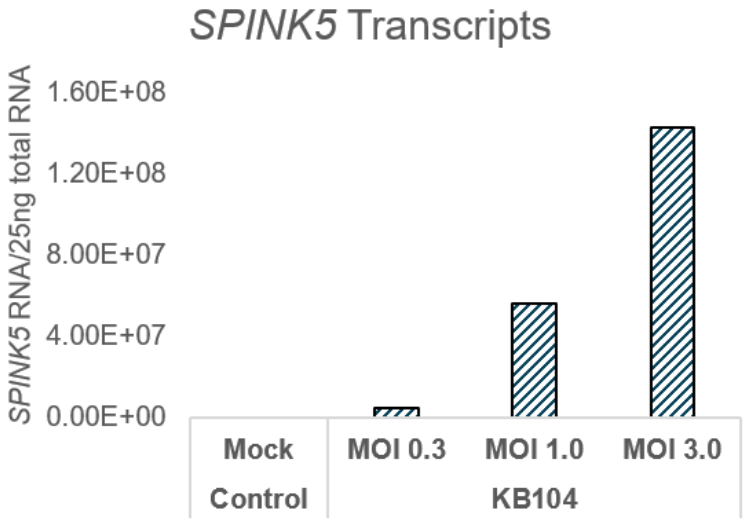
Existing approaches are limited to palliative treatments, including topical moisturizers, repair formulas, and steroids

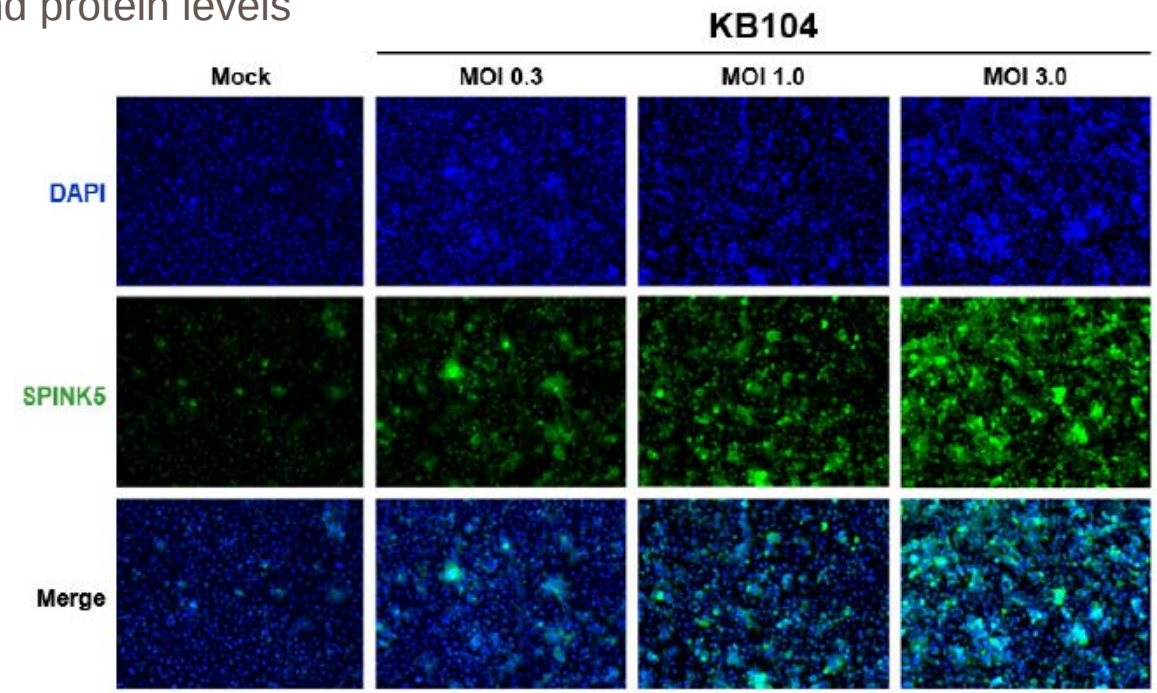
1. Orphanet Report Series, Rare Diseases collection, June 2018, Number 1;
2. Bitoun et al. *J Invest Dermatol.* 2002 118(2): 352-61;
3. Furio and Hovnanian. *Biol Chem.* 2014 395(9) 945-58; and
4. Keuylian and Hovnanian. *Biol Chem.* 2016 ;397(12):1223-1228.

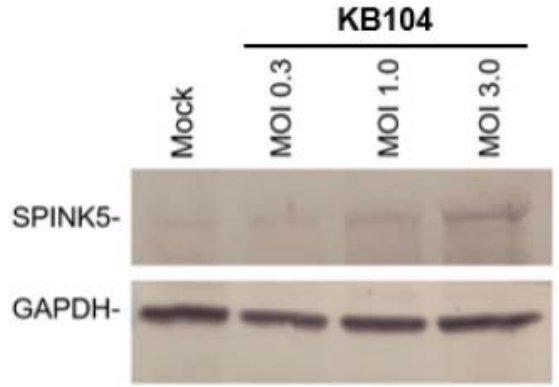
KB104 Preclinical: Immortalized Human Keratinocytes

Robust SPINK5 expression detected at the transcript and protein levels



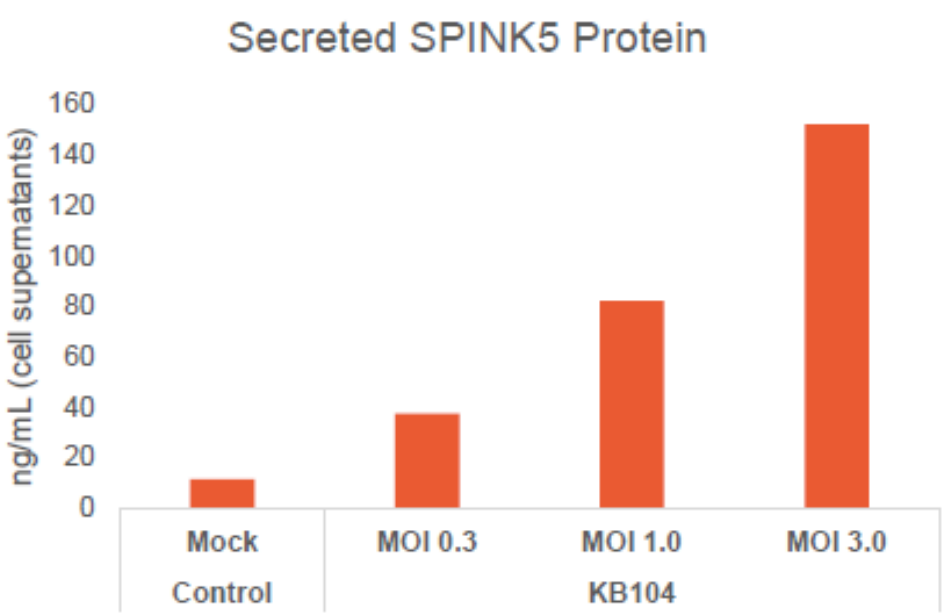




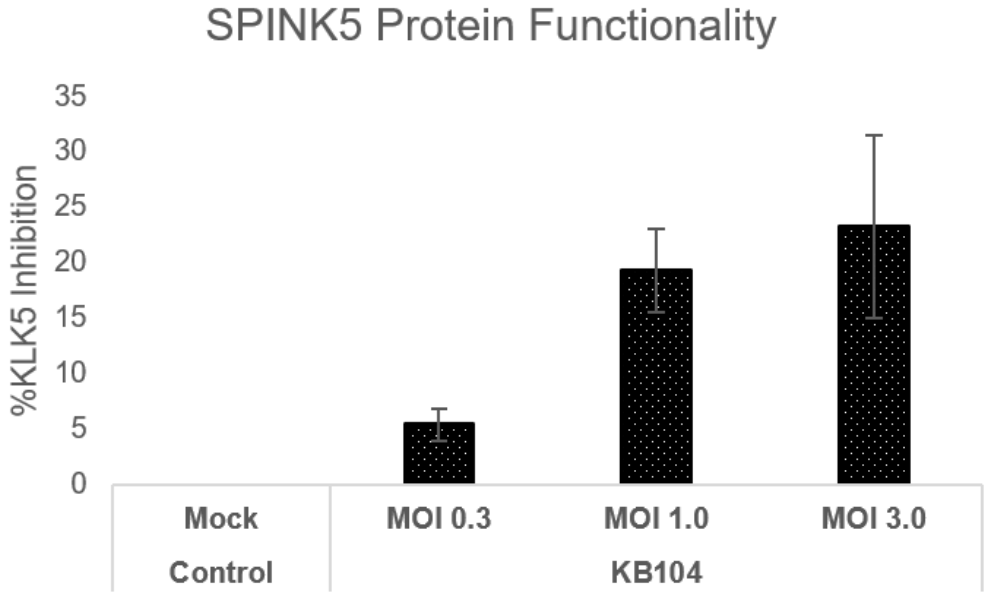


KB104 Preclinical: Immortalized Human Keratinocytes

Functional SPINK5 is secreted from transduced human keratinocytes



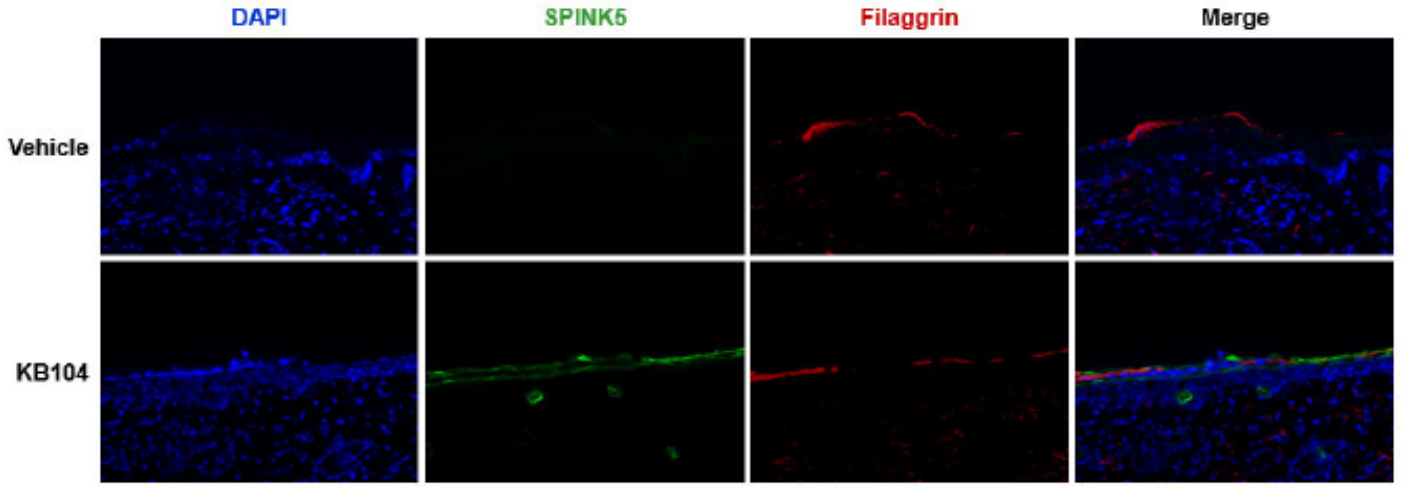
ELISA-based quantification of human SPINK5 protein secretion into the supernatant of transduced cells



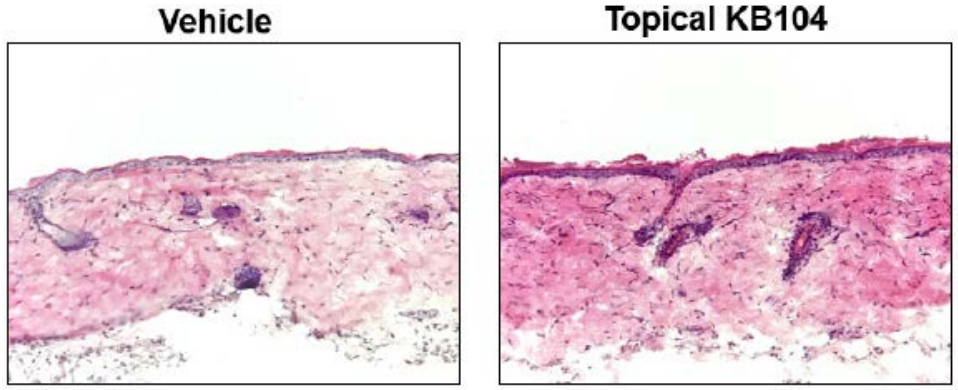
Activity of secreted SPINK5 protein assessed using an enzymatic inhibition assay measuring SPINK5's ability to inhibit its native target, the human serine protease Kallikrein 5 (KLK5)

KB104 Preclinical: *In Vivo* Single Dose Pharmacology

Properly localized human SPINK5 detected 48 hours after topical KB104 application in mice without toxicity



Filaggrin serves as a marker for the cornified layer of the epidermis - indicates that KB104-mediated human SPINK5 is expressed in the correct layer of skin



Manufacturing

Krystal

Krystal's Core Competency: CMC/Manufacturing

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

- 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

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

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

Key Opinion Leaders

Currently working with Krystal on KB103 and KB105

Dr. Peter Marinkovich

Department of Dermatology
Stanford University
Serving as lead clinical investigator in KB103 phase I/II trial

Dr. Andrew South

Department of Dermatology,
Thomas Jefferson University

Dr. Joyce Teng

MD, PhD
Clinical Professor, Dermatology Clinical Professor, Pediatrics
Stanford University

Dr. Keith Choate

MD, PhD
Professor of Dermatology,Genetics, Pathology
Yale University School of Medicine

Dr. Amy Paller

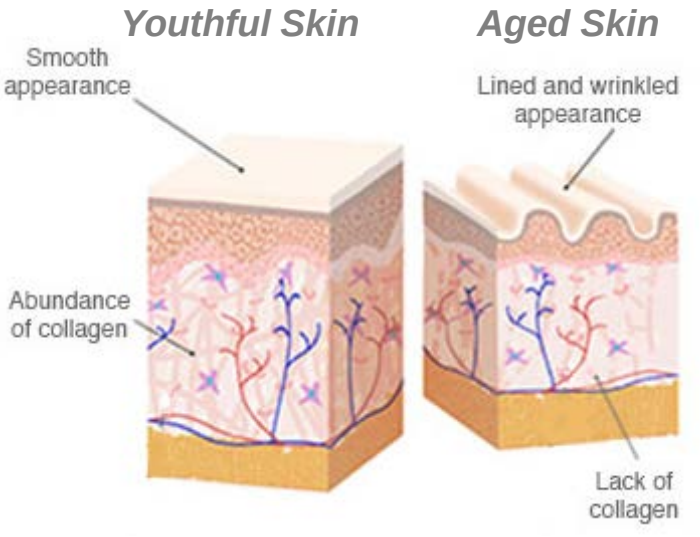
MD
Chair of Dermatology
Northwestern University

Dr. Alain Hovnanian

MD, PhD
Director, INSERM Department on Genetic Skin Diseases
University Paris Descartes – Sorbonne Paris Cité

Beyond Severe Monogenic Skin Diseases

Application of fully-integrated STAR-D platform to treat aesthetic defects



The characteristic features of skin aging are largely due to aberrant collagen homeostasis, resulting in a net collagen deficiency

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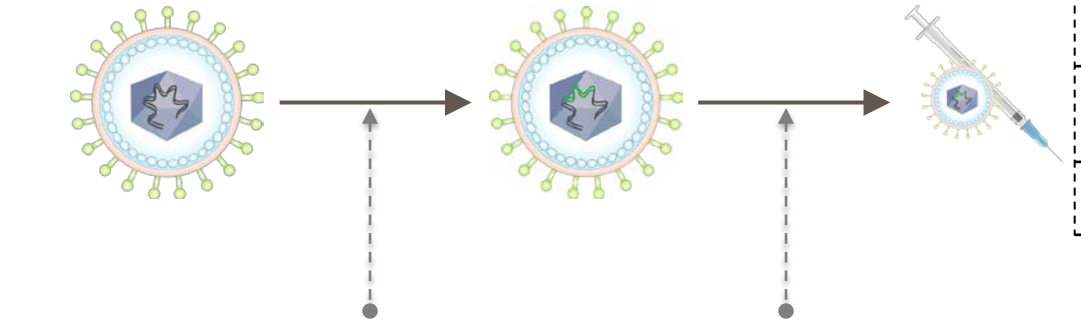
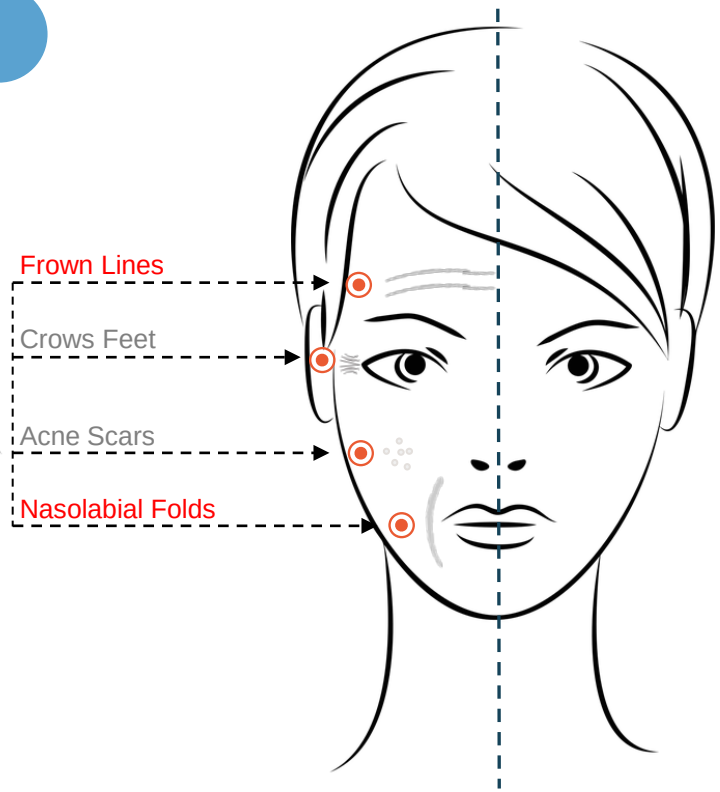
Off-the-shelf, Non-Invasive Modified HSV-1 Therapy





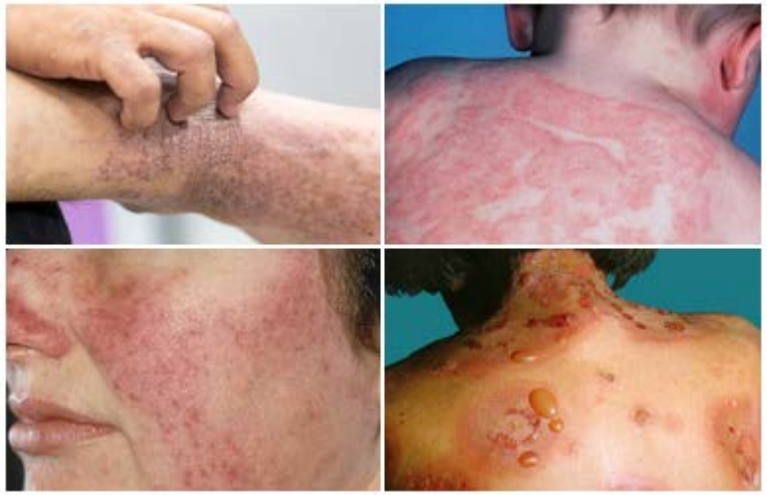
Fromowitz, J. "Update on Aging Skin"; Florida Society of Dermatology

Beyond Severe Monogenic Skin Diseases

Application of fully-integrated STAR-D platform to treat complex, chronic skin conditions

Chronic skin conditions

KB500 series (Antibodies) for Chronic Skin Diseases (Atopic Dermatitis, Psoriasis, *etc.*)



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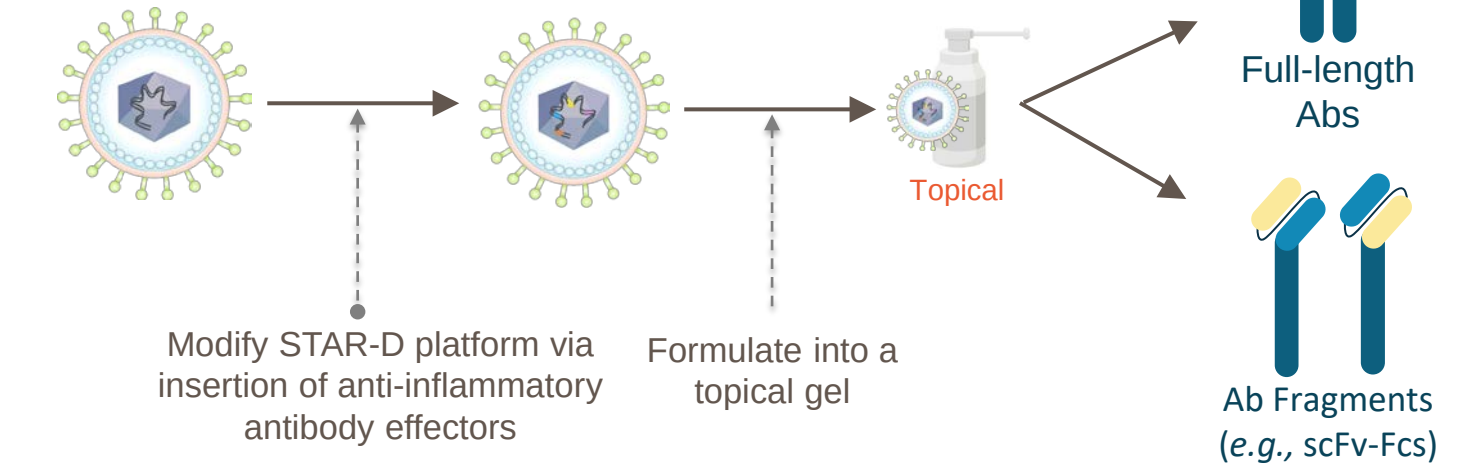
Off-the-shelf, Non-Invasive Modified HSV-1 Therapy



Krystal

Medicines for Skin Diseases and Conditions –
A Gene Therapy Company