

**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
Washington, D.C. 20549**

**FORM 8-K**

**CURRENT REPORT  
Pursuant to Section 13 or 15(d)  
of the Securities Exchange Act of 1934**

**Date of Report (Date of earliest event reported): August 9, 2021**

**KRYSTAL BIOTECH, INC.**  
(Exact name of registrant as specified in its charter)

**Delaware**  
(State or other jurisdiction  
of incorporation)

**001-38210**  
(Commission  
File Number)

**82-1080209**  
(IRS Employer  
Identification Number)

**2100 Wharton Street, Suite 701  
Pittsburgh, Pennsylvania 15203**  
(Address of principal executive offices, including Zip Code)

**Registrant's telephone number, including area code: (412) 586-5830**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	KRY5	Nasdaq Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

**Item 2.02 Results of Operation and Financial Condition.**

On August 9, 2021, Krystal Biotech, Inc., a Delaware corporation (the "Company"), announced its financial results for the quarter ending June 30, 2021. A copy of the Company's press release is attached as Exhibit 99.1 hereto and incorporated by reference herein.

The information concerning financial results in this Form 8-K and in Exhibit 99.1 shall not be deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section. The information concerning financial results in this Form 8-K and in Exhibit 99.1 shall not be incorporated into any registration statement or other document filed with the Securities and Exchange Commission by the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing, except as shall be expressly set forth by specific reference in such filing.

**Item 7.01 Regulation FD Disclosure.**

On August 9, 2021, the Company posted an updated corporate presentation to its website, www.krystalbio.com.com. A copy of the presentation is attached as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

This information in this Item 7.01 of this Current Report on Form 8-K shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that Section, or incorporated by reference in any filing.

**Item 9.01 Financial Statements and Exhibits.**

(d) Exhibits.

<u>Exhibit No.</u>	<u>Description</u>
99.1	<a href="#">Press Release, dated August 9, 2021</a>
99.2	<a href="#">Corporate Presentation dated August 2021</a>
104	Cover Page Interactive Data file (embedded within the Inline XBRL document)

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: August 9, 2021

KRYSTAL BIOTECH, INC.

By: /s/ Krish S. Krishnan

Name: Krish S. Krishnan

Title: Chairman and Chief Executive Officer

**Krystal Biotech Reports Second Quarter 2021 Financial Results and Provides Update on Operational Progress**

- Top-line data from the pivotal GEM-3 study of B-VEC in dystrophic epidermolysis bullosa (“DEB”) on track for 4Q21
- Initiation of Phase 1 study of inhaled KB407 for the treatment of cystic fibrosis expected in 3Q21
- Our wholly-owned subsidiary Jeune Aesthetics, Inc. initiated dosing in the efficacy cohort of the PEARL-1 study of intradermal KB301 for aesthetic skin conditions
- Strong balance sheet with June 30, 2021 cash, cash equivalents and marketable securities of \$389.1 million

PITTSBURGH, August 9, 2021 – Krystal Biotech Inc., (“Krystal”) (NASDAQ: KRYS), the leader in redosable gene therapies for rare diseases, today reported financial results and key operational progress updates for the second quarter ending June 30, 2021.

“We are pleased with the progress we have made this quarter on multiple fronts. Not only has the Krystal team continued to advance three clinical stage programs including the pivotal GEM-3 trial, we have also grown the commercial side of our organization and made significant headway on the construction of our 2<sup>nd</sup> GMP manufacturing facility,” said Krish S. Krishnan, Chairman and Chief Executive Officer of Krystal Biotech, Inc. “The remainder of 2021 promises to be even more exciting as we look forward to reporting pivotal data on B-VEC, Jeune announcing initial efficacy data for KB301 in aesthetic skin conditions, and initiating a Phase 1 trial to evaluate our first pulmonary candidate - KB407 for the treatment of cystic fibrosis.”

**Program Highlights & Upcoming Events:****B-VEC for DEB**

- The Company continued to advance the pivotal GEM-3 trial and is on track to announce top-line data in 4Q21. Details of the pivotal Phase 3 study can be found at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) under NCT identifier NCT04491604.



- During the second quarter the Company began enrolling patients into an open label extension (“OLE”) study, including patients who participated in the Phase 3 study and new patients who meet all enrollment criteria. Details of the OLE study can be found at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) under NCT identifier NCT04917874.

#### KB407 for Cystic Fibrosis

- Following the initial announcement of data from the GLP toxicology and biodistribution study of repeat doses of KB407 in nonhuman primates in April 2021, the Company will present more detailed results from this study in a poster at the North American Cystic Fibrosis Conference (“NACFC”), taking place September 30 - October 2.
- The Company is on track to initiate a Phase 1 study of KB407 in 3Q21.

#### KB105 for TGM1-ARCI

- In July 2021, the Company announced data from the fourth patient dosed in the Phase 1/2 trial evaluating topical KB105 for the treatment of TGM1-deficient autosomal recessive congenital ichthyosis (“TGM1-ARCI”). These data showed that repeat KB105 dosing continued to be well tolerated with no adverse events or evidence of immune response.
- Krystal plans to discuss these data with patients and key opinion leaders to help inform next steps. In particular, the Company will assess the optimal dosing frequency as well as additional clinical endpoints, including a novel scale designed for ichthyosis. The Company intends to complete these discussions by the end of the year and continue dosing in a Phase 2 trial in 2022.

#### KB301 for Aesthetic Indications

- In August 2021, Jeune Aesthetics, Inc., a wholly-owned subsidiary of Krystal Biotech Inc., announced the initiation of dosing in the efficacy cohort of the PEARL-1 (Phase 1) study of KB301 for aesthetic skin indications. Details of the Phase 1 study can be found at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) under NCT identifier NCT04540900.
- Initial efficacy data from this study is anticipated in 4Q21.

#### **Financial results for the quarter ended June 30, 2021:**

- Cash, cash equivalents, and marketable securities totaled \$389.1 million on June 30, 2021, compared to \$271.3 million as of December 31, 2020.
- Research and development expenses for the second quarter ended June 30, 2021 were \$6.6 million, compared to \$3.6 million for the second quarter 2020, and \$12.8 million for the six months ended June 30, 2021, compared to \$7.2 million for the six months ended June 30, 2020.

- General and administrative expenses for the second quarter ended June 30, 2021 were \$9.8 million, compared to \$3.3 million for first quarter 2020, and \$18.0 million for the six months ended June 30, 2021, compared to \$5.7 million for the six months ended June 30, 2020.
- Net losses for the quarters ended June 30, 2021 and 2020 were \$16.4 million and \$6.8 million, or \$(0.74) and \$(0.37) respectively, per common share (basic and diluted). Net losses for the six months ended June 30, 2021 and 2020 were \$32.2 million and \$12.2 million or \$(1.48) and \$(0.68), respectively, per common share (basic and diluted)
- For additional information on the Company's financial results for the second quarter ended June 30, 2021, refer to form 10-Q filed with the SEC.

#### ***About Krystal Biotech***

Krystal Biotech, Inc. (NASDAQ:KRY5) is a pivotal-stage gene therapy company leveraging its novel, redosable gene therapy platform and in-house manufacturing capabilities to develop therapies to treat serious rare diseases. For more information please visit <http://www.krystalbio.com>.

#### ***Forward-Looking Statements***

Any statements in this press release about future expectations, plans and prospects for Krystal Biotech, Inc., including but not limited to statements about the development of Krystal's product candidates, such as plans for the design, conduct and timelines of ongoing pre-clinical and clinical trials of beremagene geperpavec ("B-VEC"), KB105, KB104, KB301, KB407, and KB408; the clinical utility of B-VEC, KB105, KB104, KB301, KB407 and KB408, and Krystal's plans for filing of regulatory approvals and efforts to bring B-VEC, KB105, KB104, KB301, KB407 and KB408 to market; the market opportunity for and the potential market acceptance of B-VEC, KB105, KB104, KB301, KB407 and KB408; plans to pursue research and development of other product candidates; the sufficiency of Krystal's existing cash resources; the unanticipated impact of COVID-19 on Krystal's business operations, pre-clinical activities and clinical trials; 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 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 trials 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 including B-VEC, KB105, KB104, KB301, KB407 and KB408, the sufficiency of cash resources and need for additional financing and such other important factors as are set forth under the caption "Risk Factors" in Krystal's annual and quarterly reports on file with the U.S. Securities and Exchange Commission. In addition, the forward-looking statements included in this press release represent Krystal's views as of the date of this release. Krystal anticipates that subsequent events and developments will cause its views to change. However, while Krystal 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 Krystal's views as of any date subsequent to the date of this release.

**CONTACTS:**

**Investors:**

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**Media:**

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**Consolidated Balance Sheet Data:**

(In thousands)	June 30, 2021	December 31, 2020
<b>Balance sheet data:</b>		
Cash and cash equivalents	\$329,527	\$ 268,269
Working capital	351,808	259,606
Total assets	443,556	310,844
Total liabilities	25,016	18,760
Total stockholders' equity	\$418,540	\$ 292,084

**Consolidated Statement of Operations:**

(In thousands, except shares and per share data)	Three Months Ended June 30,		Change
	2021	2020	
<b>Expenses</b>			
Research and development	\$ 6,594	\$ 3,639	\$ 2,955
General and administrative	9,799	3,315	6,484
Total operating expenses	16,393	6,954	9,439
Loss from operations	(16,393)	(6,954)	(9,439)
<b>Other Income (Expense)</b>			
Interest and other income, net	30	121	(91)
Total other income (expense)	30	121	(91)
Net loss	\$ (16,363)	\$ (6,833)	\$ (9,530)
Net loss per common share: Basic and diluted	\$ (0.74)	\$ (0.37)	
Weighted-average common shares outstanding: Basic and diluted	22,204,659	18,383,941	

(In thousands, except shares and per share data)	Six Months Ended June 30,		Change
	2021	2020	
<b>Expenses</b>			
Research and development	\$ 12,795	\$ 7,164	\$ 5,631
General and administrative	17,951	5,735	12,216
Total operating expenses	30,746	12,899	17,847
Loss from operations	(30,746)	(12,899)	(17,847)
<b>Other Income (Expense)</b>			
Interest and other income, net	64	725	(661)
Build to suit interest expense	(1,492)	—	(1,492)
Total other income (expense)	(1,428)	725	(2,153)
Net loss	\$ (32,174)	\$ (12,174)	\$ (20,000)
Net loss per common share: Basic and diluted	\$ (1.48)	\$ (0.68)	
Weighted-average common shares outstanding: Basic and diluted	21,731,711	17,871,648	



Source: Krystal Biotech, Inc.



The Leader in Redosable Gene Therapy for Rare Disease

August 2021

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## 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 beremagene geperpavec (“B-VEC”), KB105, KB104, KB301, KB407, and KB408 and the Company’s other product candidates; conduct and timelines of preclinical and clinical trials, the clinical utility of B-VEC, KB105, KB104, KB301, KB407 and KB408 and the Company’s other product candidates; plans for and timing of the review of regulatory filings, efforts to bring B-VEC, KB105, KB104, KB301, KB407 and KB408 and the Company’s other product candidates to market; the market opportunity for and the potential market acceptance of B-VEC, KB105, KB104, KB301, KB407 and KB408 and the Company’s other product candidates, the development of B-VEC, KB105, KB104, KB301, KB407 and KB408 and the Company’s other product candidates for additional indications; the development of additional formulations of B-VEC, KB105, KB104, KB301, KB407 and KB408 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.

# Krystal overview

A fully integrated, clinical stage gene therapy company powered by proprietary redosable gene delivery platform

## Differentiated viral vector platform enables *in vivo*, repeat dose gene therapies

- Proprietary, engineered *replication incompetent* HSV-1 based platform
- Clinical data shows maintenance of safety and transgene expression after repeat dosing
- Positive external clinical and regulatory precedent with *in vivo* HSV-1 based therapy

## Initial focus on rare, dermatologic indications led to rapid clinical proof of concept and pipeline

- Lead program, B-VEC (formerly KB103) went from IND to Phase 3 in less than 3 years; pivotal data anticipated in 4Q21
- Two lead dermatologic pipeline programs, KB104 and KB105, leverage the same vector

## Broadening focus to address larger indications and new tissue types

- Ongoing Phase 1 trial in aesthetic skin indications with KB301, under our wholly owned subsidiary Jeune Aesthetics, Inc.
- Positive pre-clinical data from KB407 for cystic fibrosis demonstrates potential to target lung tissue
- Continue to drive innovation by investing in next-gen platform capabilities

## In-house GMP manufacturing to support clinical and commercial needs

- Stable producer cell line developed and leveraged across pipeline has cost, scale, and regulatory benefits
- Current GMP facility near company headquarters in Pittsburgh is producing pivotal material at commercial scale; BLA readiness is underway
- Investing in additional capacity via construction of an ~150,000 sqft facility which is expected to be operational in 2022

## Upcoming Milestones

Timing	Program	Event
✓ 1Q21	B-VEC for DEB	Complete enrollment in pivotal GEM-3 study in DEB
✓ 1Q21	KB301 for aesthetic indications	Announce Initial safety data from cohort 1 of Phase 1 study in facial wrinkles and acne scars
✓ 1Q21	KB301 for aesthetic indications	Provide update on strategy for KB301 and aesthetic pipeline (under Jeune Aesthetics, Inc.)
✓ 2Q21	KB407 for CF	Announce data from IND enabling toxicology study in nonhuman primates
✓ 2Q21	Respiratory pipeline	Announce development candidate for new genetic lung disease
✓ 2Q21	B-VEC	Present detailed Phase 1/2 safety summary at SID (May 3-8)
✓ 2Q21	KB301	Present detailed Phase 1 (cohort 1) safety summary at SID (May 3-8)
✓ 2Q21	KB5XX	Present preclinical proof-of-concept from vectorized antibody platform at ASGCT (May 11-14)
✓ 2Q21	KB105 for TGM1-ARCI	Announce initial Phase 2 data and update on next Phase 2 cohorts
3Q21	KB407 for CF	Initiate Phase 1/2 study
2H21	KB301 for aesthetic indications	Initial efficacy data from Phase 1 study
3Q21/4Q21	KB407 for CF	Present nonhuman primate GLP tox data at NACFC (9/30-10/2)
<b>4Q21</b>	<b>B-VEC for DEB</b>	<b>Announce top line data from the pivotal GEM-3 study</b>
2022	KB105 for TGM1-ARCI	Initiate dosing in next Phase 1/2 cohort
2022	KB104 for Netherton	File IND and initiate clinical trial

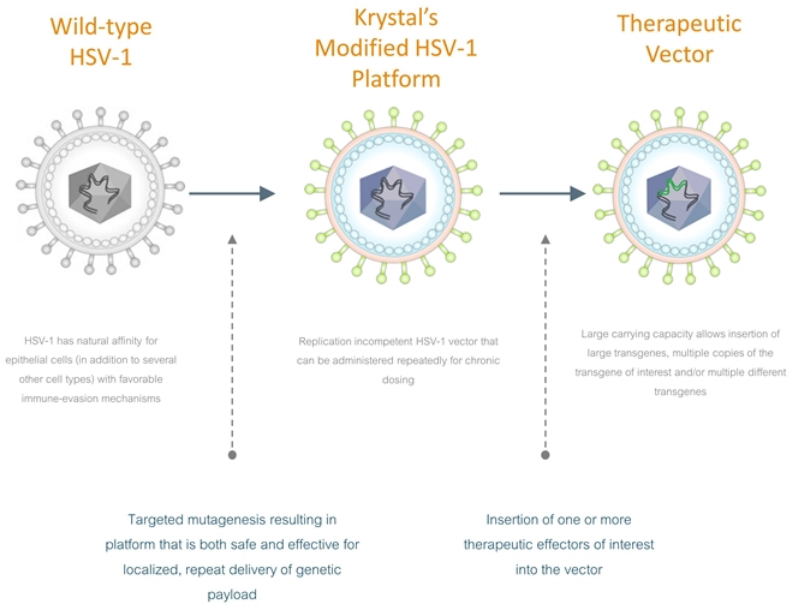
All pipeline compounds are investigational, being evaluated in clinical or pre-clinical studies.



**Our technology platform enables  
noninvasive, redosable gene therapy**



# HSV-1 is positively differentiated vs. other gene therapy technologies



## Vector Platform Comparison

	LV	AAV	HSV-1	LNP
<b>In vivo dosing?</b>	No	Yes	<b>Yes</b>	Yes
<b>Baseline antibody exclusion criteria?</b>	No (if <i>ex vivo</i> )	Yes	<b>No</b>	No
<b>Repeat-dose capabilities?</b>	Yes (if <i>ex vivo</i> )	No	<b>Yes</b>	Yes
<b>Carrying capacity?</b>	8 kb <sup>1</sup>	<4 kb <sup>1</sup>	<b>&gt;30 kb</b>	~12 kb <sup>2</sup>
<b>Integrates payload into host cell DNA?</b>	Yes	No	<b>No</b>	No
<b>Regulatory precedent?</b>	Yes	Yes	<b>Yes</b>	Yes

1. Lundstrom, K. Viral Vectors in Gene Therapy. *Diseases* 2018, 6, 42.  
 2. Generation Bio (GBIO) Prospectus. (2020, June 11). Retrieved September 4, 2020.  
<https://www.sec.gov/Archives/edgar/data/1733294/000119312520167812/d924849d424b4.htm>

LV = lentivirus  
 AAV = adeno-associated virus  
 LNP = lipid nanoparticle

# Therapeutic pipeline

	Product	Protein	Indication	Discovery	Preclinical	Phase 1/2	Phase 3	Key Upcoming Milestone	Ownership
Dermatology	<b>B-VEC</b> <sup>†•Δ‡§</sup>	Type VII collagen (COL7)	Dystrophic EB	→			→	Top line Phase 3 data in 4Q21	Wholly owned
	<b>KB105</b> <sup>†•‡</sup>	Transglutaminase 1 (TGM1)	TGM1-deficient ARCI	→			→	Initiate next Phase 2 cohort in 2022	Wholly owned
	<b>KB104</b> <sup>‡</sup>	Serine Peptidase Inhibitor Kazal Type 5 (SPINK5)	Netherton Syndrome	→				File IND in 2022	Wholly owned
	<b>KB1XX</b>	Undisclosed programs		→					Wholly owned
	<b>KB5XX</b>	Vectorized antibodies	Chronic conditions	→					Wholly owned
Respiratory	<b>KB407</b> <sup>†•‡</sup>	Cystic fibrosis transmembrane conductance regulator (CFTR)	Cystic fibrosis	→				Initiate Phase 1 study in 3Q21	Wholly owned
	<b>KB408</b>	Alpha-1 antitrypsin (AAT)	Alpha-1 antitrypsin deficiency	→					Wholly owned
	<b>KB4XX</b>	Undisclosed programs		→					Wholly owned

All pipeline compounds are investigational, being evaluated in clinical or pre-clinical studies.

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

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Program	Indication	Gene	Discovery	IND Enabling	Clinical Development	Next Milestone
KB301	Skin quality	type III collagen (COL3)				Phase I efficacy data in 4Q21
KB302	TBA	type I collagen (COL1)				
KB303	TBA	elastin (ELN)				
KB304	TBA	COL3 + ELN				

All pipeline compounds are investigational, being evaluated in clinical or pre-clinical studies.

# Platform supported by in-house manufacturing capacity and expertise

## 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

## Upstream process using stable producer cell lines has cost and regulatory benefits

- Stable complementary cell lines developed in-house are used in established methods for production of consistent batches
- Eliminates the need for multiple cGMP qualifications of plasmids and variability in transfection efficiency from batch to batch
- Scalable from clinical phase to commercial

## We have successfully developed a robust and reproducible downstream process

- Work conducted in an aseptic closed system process
- The same process is leveraged across pipeline with minimal redevelopment effort between product candidates
- Compliant with global regulatory requirements



**Initial focus on rare skin diseases led to rapid clinical POC and pipeline**



# Dystrophic epidermolysis bullosa (DEB)

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

## Dystrophic Epidermolysis Bullosa

- A rare, genetic skin disease that causes skin to tear or blister from minor contact
- Mutations in the *COL7A1* gene lead to absent or dysfunctional COL7 protein, without which the epidermis does not anchor to the dermis
- The recessive form (RDEB) is the classic, most severe form of the condition. Dominant DEB (DDEB) has a broader range in severity and is often characterized by blistering on the hands, feet, knees, and elbows



## Epidemiology

- **Prevalence:** Up to 125,000 people are affected by DEB worldwide<sup>1</sup>
- We believe that there are, at present, approximately 3,000 DEB patients in the US
- **Incidence:** The incidence of DEB is 6.5 per million births in the US<sup>2</sup>

## Current Standard of Care

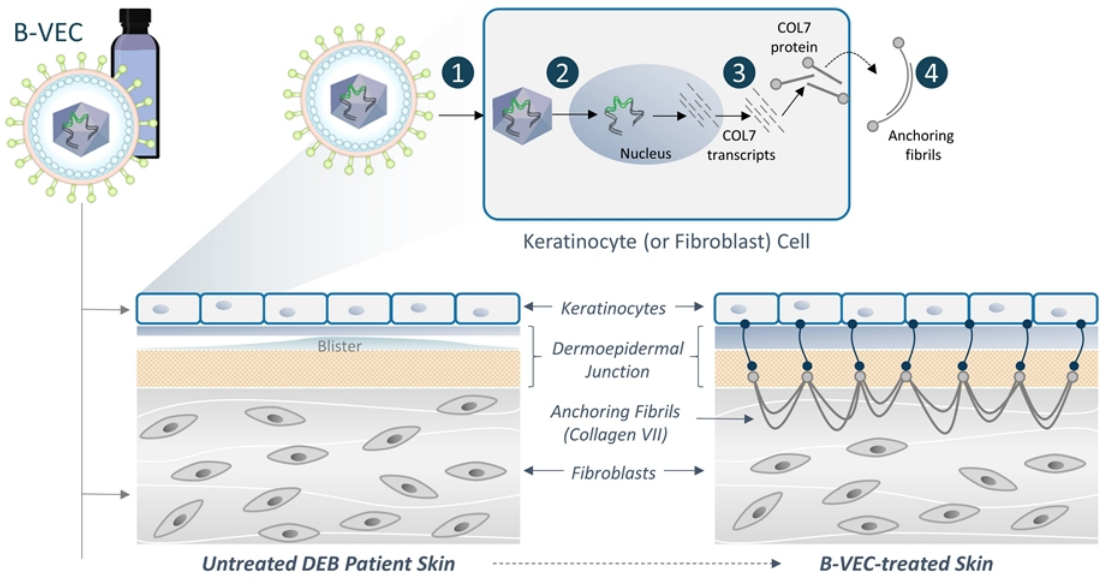
- There are no approved treatments for DEB
- Existing therapies limited to expensive and time-consuming palliative treatments
- Palliative treatments cost \$200k – \$400k annually<sup>3,4</sup>

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](http://cordis.europa.eu/result/rcn/156078_en.html)



# Beremagene geperpavec (B-VEC) for DEB

Topically applied B-VEC gel is designed to induce local COL7 expression and molecular correction





# Topical B-VEC was evaluated in a Phase 1/2 study

## Design

- GEM1/2 (NCT03536143) was an intra-patient comparison of wounds randomized to receive either topical B-VEC or placebo.
- Each patient on-study for ~6 months; 3 months of on-site visits followed by 3-month at-home imaging period
- Study PI: Dr. Peter Marinkovich (Stanford University)

## Enrollment

- A total of 9 RDEB patients (adult and pediatric) were enrolled in the study; 3 subjects re-enrolled later in the study and were re-randomized for a total of 12 subjects

## Dosing

- In the Ph1 portion (n=2) one wound was administered B-VEC and one wound was administered placebo at a dose of 1e8 PFU/wound with varying frequency throughout the study period
- In Phase 2 portion (n=10) 2 wounds were administered B-VEC and one wound was administered placebo (except 1 patient who was 1:1) at doses of either 2e8, 3e8, 6e8 or 8e8 PFU/wound with varying frequency throughout the study period

## Key Endpoints

### Safety measures

- 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

### Efficacy measures

- Level of collagen VII (COL7) in B-VEC-administered skin as measured by immunofluorescence; presence of anchoring fibrils as measured by immunoelectron microscopy
- Wound closure (change in wound surface area relative to baseline), time to wound closure, and duration of wound closure, all relative to placebo

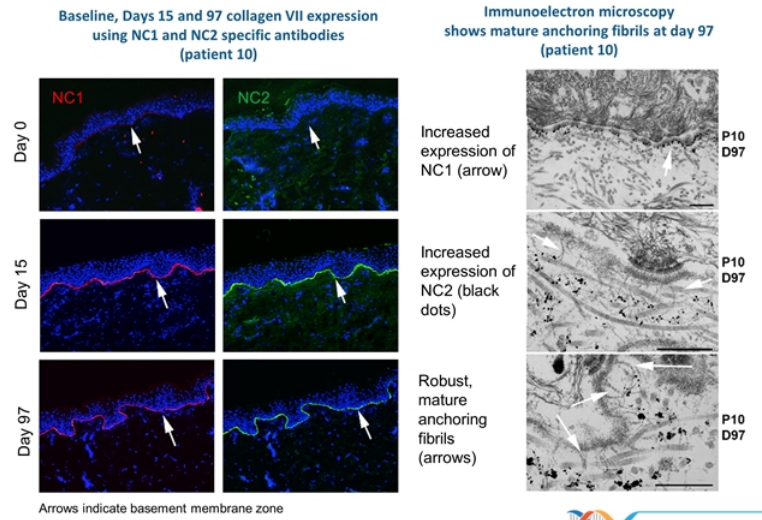
# Repeat doses of topical B-VEC were well tolerated; COL7 expression and molecular correction established

## Increasing doses and dosing frequency were well tolerated

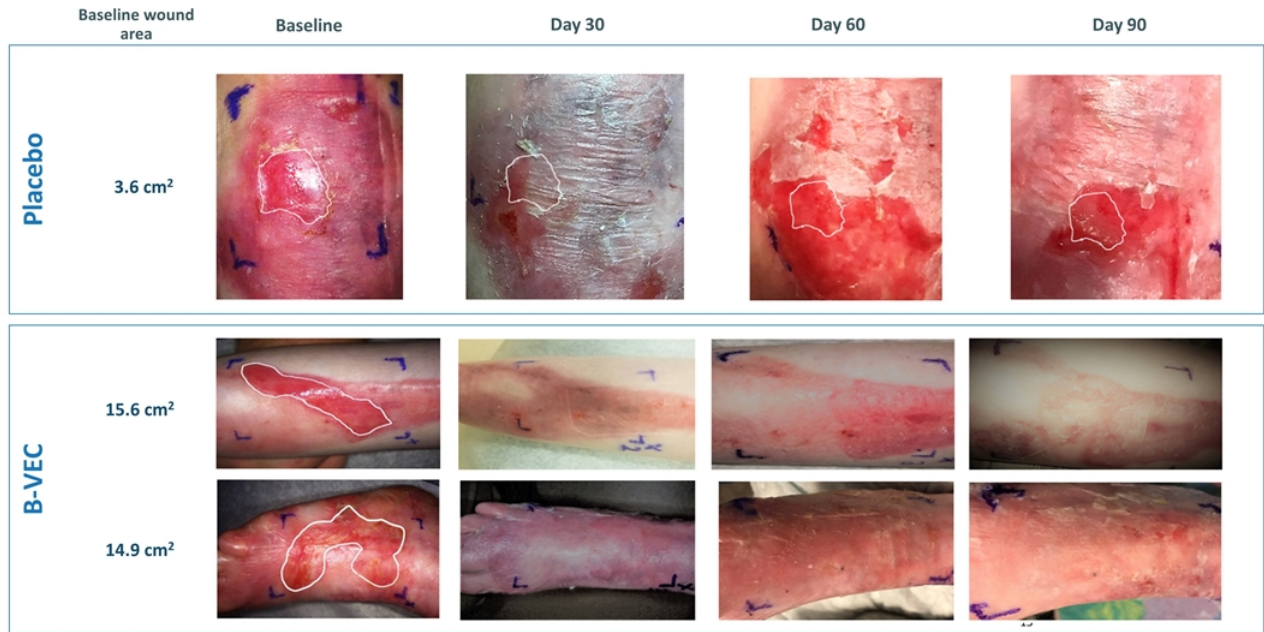
- In the Ph1/2 trial, the number of repeat doses per wound ranged from 4 to 41; the PFU per wound ranged from 1e8 to 8e8
- No treatment-related serious AEs were reported; AEs deemed possibly related were mild (n=20) or moderate (n=1)
- No immune response or blistering observed around the sites of administration following first and repeat doses
- Blood and urine samples collected throughout the study revealed:
  - No systemic viral shedding
  - No adverse events associated with routine labs (chemistry and hematology)
- Some patients had baseline COL7 and/or HSV-1 antibodies which did not impair efficacy or impact tolerance of therapy

## Molecular correction established and correlated with wound healing

- Expression and correct localization of full-length COL7 was observed following B-VEC therapy, evidenced by presence of *both* NC1 and NC2 domains and visible anchoring fibrils on IEM.



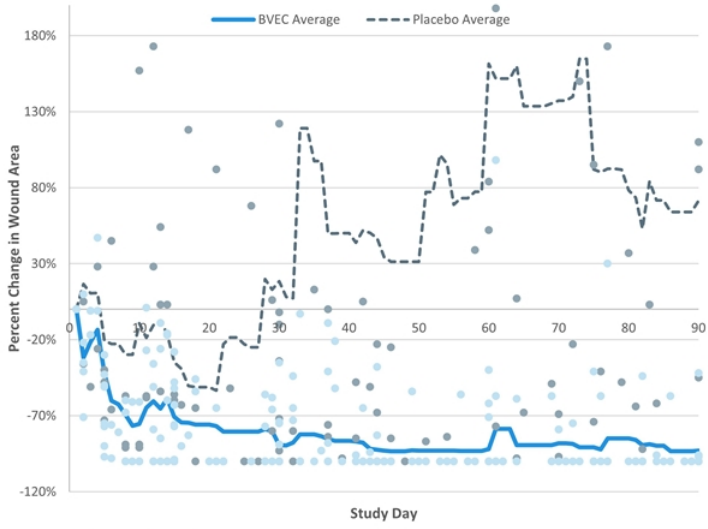
# Time course of B-VEC vs. placebo treated wounds - patient 5 (age 13)



Dose:  $3 \times 10^8$  PFU per dose  
Dosing days: 1, 2, 3, 4, 5, 36

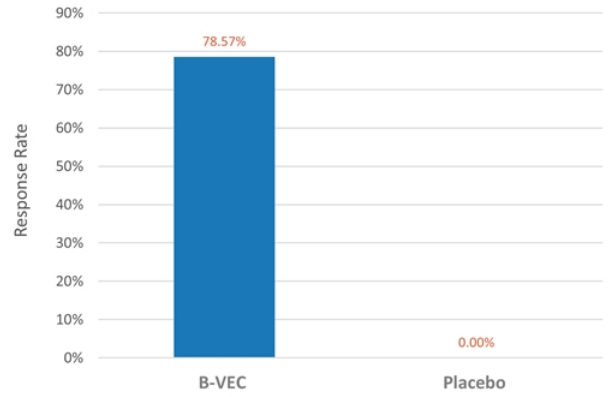
# B-VEC showed statistically significant benefit in wound healing relative to placebo

Percent change in wound area from (individual measurements and average) from Day 0 to 90<sup>†</sup>



\*excluding patient 12

78.6% of B-VEC treated wounds vs. 0% of placebo treated wounds were completely closed at weeks 8 and 10 or weeks 10 and 12<sup>‡</sup>



B-VEC	78.57% (11/14)	0.00% (0/7)
p-value*	0.00257	

\*based on McNemar test

‡analysis based on all wounds that had measurements at weeks 8 and 10 or weeks 10 and 12

# The pivotal GEM-3 study is ongoing; top line data expected in 4Q21

## Design

- GEM-3 (NCT04491604) is a randomized, double-blind, intra-patient comparison of wounds randomized to receive either topical B-VEC or placebo
- Each patient on-study for approximately 7 months: the 6-month dosing period followed by a 30-day safety follow up

## Enrollment

- 31 DEB subjects (adult and pediatric) were enrolled in US
- Ages ranged from 1 to 44 years old, 61% of patients were 18 years old or younger
- Each subject provided at least 1 pair of primary target wounds, one wound of the pair was randomized to B-VEC and the other to placebo
- In addition to the primary target wound pair(s), additional wounds (secondary wounds) may be selected to be treated with B-VEC in an open-label manner

## Efficacy Endpoints

### Primary

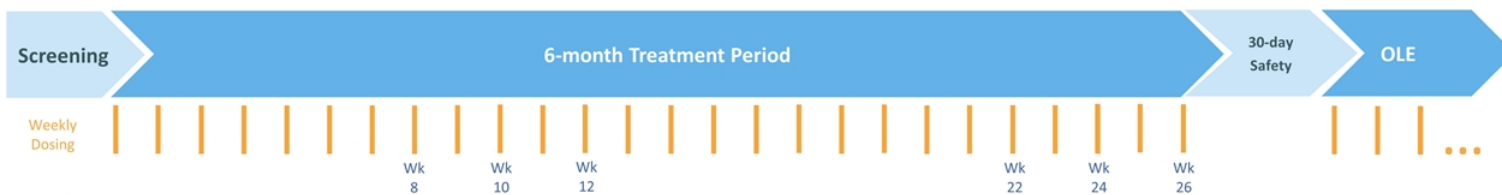
- Complete wound healing determined by the Investigator in B-VEC treated wounds versus placebo. A positive response is defined as:
  - Complete wound healing at Week 22 and Week 24; or
  - Complete wound healing at Week 24 and Week 26

### Secondary

- Complete wound healing, determined by the Investigator, as compared to baseline in B-VEC treated wounds versus placebo at weeks 8 and 10, or 10 and 12
- Mean change in pain severity (using either a VAS or FLACC-R Scale) per primary wound site associated with wound dressing changes
- Mean Change in Quality of Life in addition to Skindex score as compared to baseline at week 26

# Phase 3 trial is well powered and inclusive of a broad patient population

The trial is designed to maximize chances of success while maintaining potential for a broad label, inclusive of **chronic and recurring wounds of any size in RDEB or DDEB patients**



## Dosing:

- Primary wounds will be treated once weekly with a fixed dose until wound closure; should a wound re-open, weekly dosing will resume at the assigned dose until wound closure
- Each patient is allowed a maximum weekly dose of B-VEC; if that maximum is not reached in dosing primary wounds, additional secondary wounds may be chosen and treated with B-VEC in an open label manner

## Key Design Elements:

- No restriction on chronic or recurring wounds
- Maximum weekly dose allows for flexibility to treat multiple and / or larger wounds
- Inclusive of RDEB and DDEB patients

## Primary Endpoint:

- A positive response is defined as complete wound healing at weeks 22 and 24 or weeks 24 and 26
- The study has greater than 90% power to detect a 50% difference in response rate between B-VEC and placebo with two-sided Type 1 error rate of 5% using the McNemar test

Dose Per Wound	
Wound Area	Dose
<20cm <sup>2</sup>	4x10 <sup>8</sup> PFU
20-40cm <sup>2</sup>	8x10 <sup>8</sup> PFU
40-60cm <sup>2</sup>	1.2x10 <sup>9</sup> PFU

Maximum Weekly Dose Per Subject:	
Age	Max Weekly Dose
≥ 6 months to < 3 years	1.6x10 <sup>9</sup> PFU/week
≥ 3 years to < 6 years	2.4x10 <sup>9</sup> PFU/week
≥ 6 years	3.2x10 <sup>9</sup> PFU/week

# Autosomal Recessive Congenital Ichthyosis associated with TGM1 mutations

*Transglutaminase-1 deficiency is associated with increased mortality in the neonatal period and has a dramatic impact on quality of life*

## Autosomal Recessive Congenital Ichthyosis (ARCI) Associated with TGM1

- The most common form of ARCI is caused by an inactivating mutation in the TGM1 gene encoding the enzyme transglutaminase-1, a protein that is essential for the proper formation of the skin barrier
- The condition is characterized by thick, dry, scaly skin, increased trans-epidermal water loss (TEWL), risk for dehydration, sepsis, skin malignancies, etc



## Epidemiology<sup>1-8</sup>

- **Prevalence:** There are approximately 20,000 people affected by TGM1 related ichthyosis worldwide (~1,800 US; 3,000 EU; 18,000 ROW)
- **Incidence:** It is estimated that around 350-400 babies are born with the condition each year, worldwide

## Current Standard of Care

- There are no approved treatments for ARCI associated with TGM1
- Topical and systemic retinoids and time-consuming supportive treatments (up to 4 hours a day of skin care) are most often used

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.

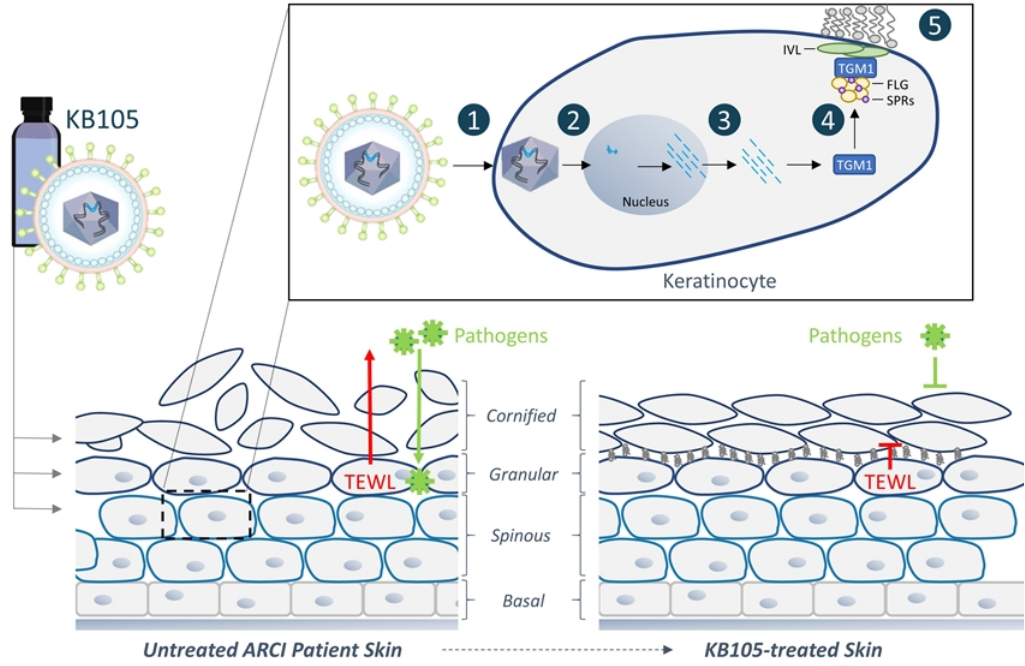
5. Pigg et al. *Acta Derm Venereol.* 2016 Nov 2;96(7):932-937;  
6. Orphanet;  
7. Foundation for Ichthyosis & Related Skin Types (FIRST);  
8. National Organization for Rare Disorders (NORD).



# KB105 for TGM1 associated ARCI

Topically applied KB105 delivers multiple copies of the human transglutaminase 1 ("TGM1") gene

- 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 is being evaluated in a Phase 1/2 study

## Design

- The Ph1/2 trial (NCT04047732) is an open label, intra-patient comparison of KB105 and placebo
- Each patient on-study for four to six months
- Study PI: Dr. Amy Paller (Northwestern University)

## Enrollment

- 4 TGM1-ARCI subjects were enrolled across 2 sites; three Ph1 patients were enrolled at Paddington Testing Company (Philadelphia); one Ph2 subject was enrolled at Northwestern (Chicago)

## Dosing

- In the Ph1 portion (n=3) one or two ~20cm<sup>2</sup> target areas were administered placebo, and 3 target areas were administered 2x10<sup>9</sup> PFU with varying frequency over ~60 days
- In Ph1, topical and microneedle administration was evaluated; in Ph2 topical administration will be utilized
- In the Phase 2 portion (n=1) four ~100cm<sup>2</sup> treatment areas were administered KB105, either 4x10<sup>9</sup> PFU or 1x10<sup>10</sup> at either a high or low dosing frequency

## Key Endpoints

### Safety measures

- AEs, including clinically significant changes in laboratory results, vitals, and physical exam findings
- Viral shedding analyzed through the collection of blood, urine, and skin swabs; antibodies to HSV and TGM1 analyzed through collection of serum

### Efficacy measures

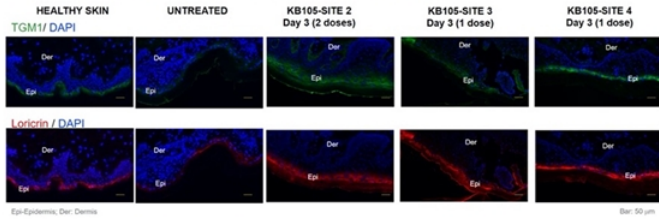
- Level of transglutaminase 1 in KB105-administered skin as measured by immunofluorescence microscopy (Ph1)
- Improvement of disease severity in the treatment area assessment through Investigator's Global Assessment (IGA)

# Phase 1/2 data shows repeat dosing of KB105 to be well tolerated; molecular and phenotypic improvement evident

## KB105 Was Well Tolerated and Generated Functional TGM1 protein

- 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
- Biopsies assessed in the Phase 1 portion of the study show:
  - KB105 treatment restored functional TGM1 protein expression and activity in all treated sites
  - KB105-expressed TGM1 was correctly localized in the epidermis, colocalizing with Lorincrin, and was functionally active
  - qPCR, IF, and in situ analyses demonstrated similar delivery efficacy of TGM1 DNA from single and repeat administration

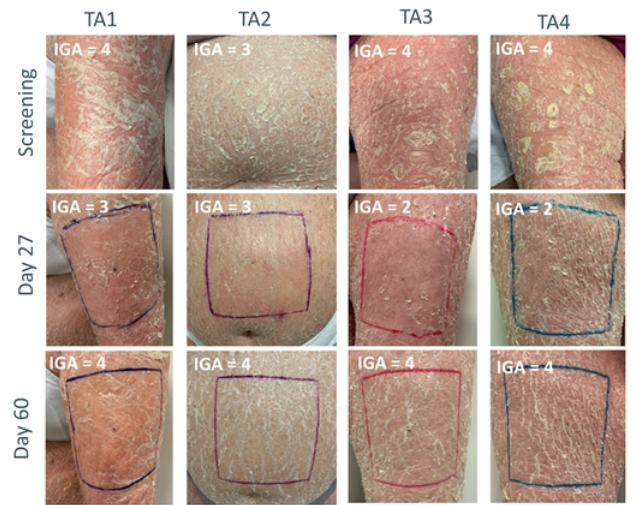
### Subject 1: Treatment Restored TGM1 Expression to Normal Levels



- TGM-1 turnover was observed to be variable and rapid, and pharmacokinetic data suggested that the optimal dosing frequency may be more frequent

## Maximum 2-point Improvement in IGA Scale as Compared to Screening Observed at Day 27 at High Dose

- In the Phase 2 portion (n=1) four ~100cm<sup>2</sup> treatment areas (TAs) were administered KB105, either 4x10<sup>9</sup> PFU or 1x10<sup>10</sup> at either a high or low dosing frequency

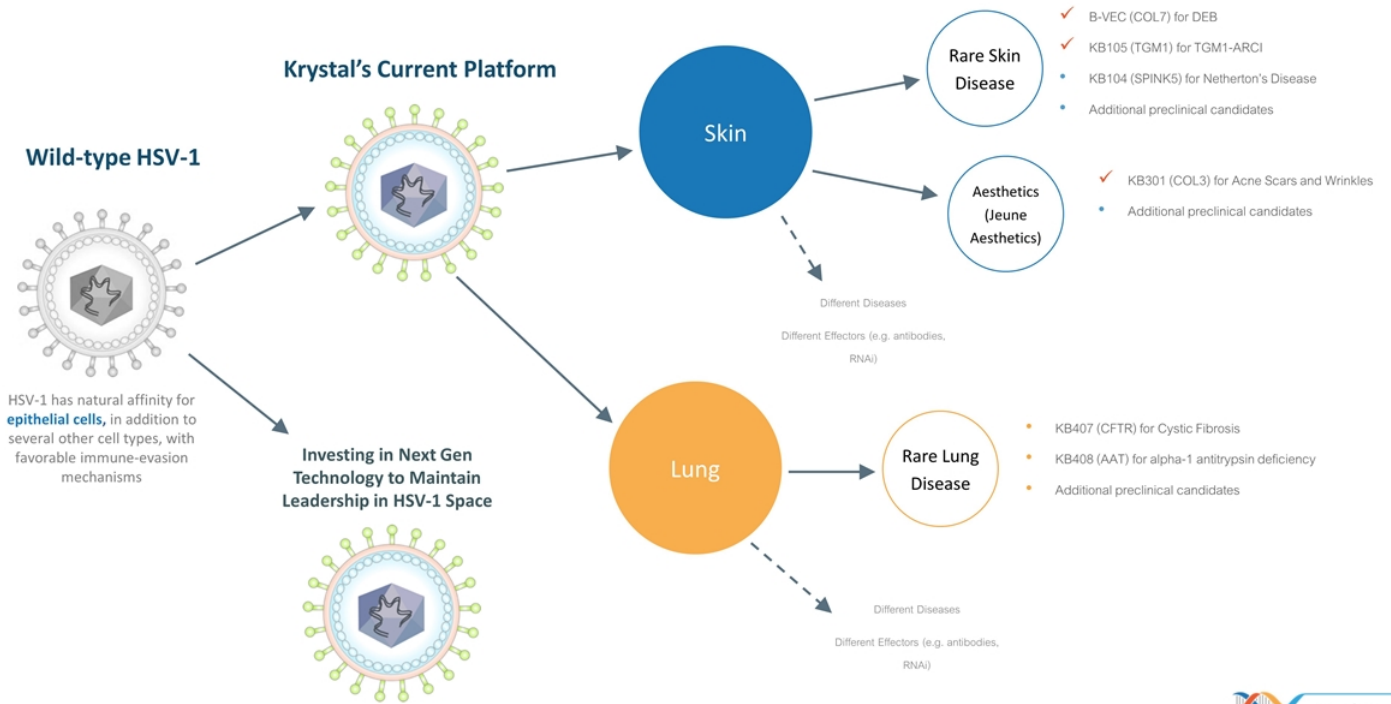


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**Leveraging platform to target new tissues and larger indications**



# HSV-1 has potential beyond rare skin diseases



# KB407 for cystic fibrosis

## Gene therapy approaches have been tried and failed in their attempts to replace CFTR protein

- Viral (adenovirus and AAV) and non-viral (DNA plasmids and stabilized mRNA) approaches have been tested in more than 25 clinical trials enrolling >470 patients
- 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

## We are developing KB407 as an inhalable, repeat dose gene therapy that delivers the full human CFTR gene

- ✓ Replication incompetent HSV-1
- ✓ Delivers two copies of full length, human CFTR protein (mutation agnostic approach)
- ✓ Duration of nebulization expected to be under 30 minutes, using a commercially available nebulizer
- ✓ Episomal delivery of CFTR gene does not disrupt cell DNA
- ✓ Ability to re-dose and/or adjust dose over time as lung cells turnover

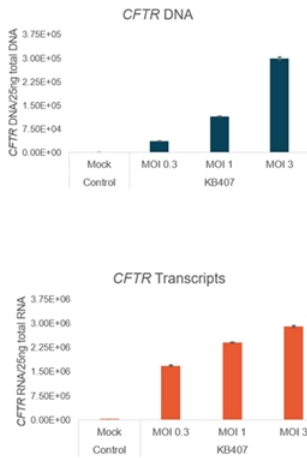
## Our vector can be formulated and delivered via nebulizer with no significant change in activity

- In vitro data shows KB407 can be nebulized, successfully transduce target lung cells and induce expression of fully functional and properly localized CFTR

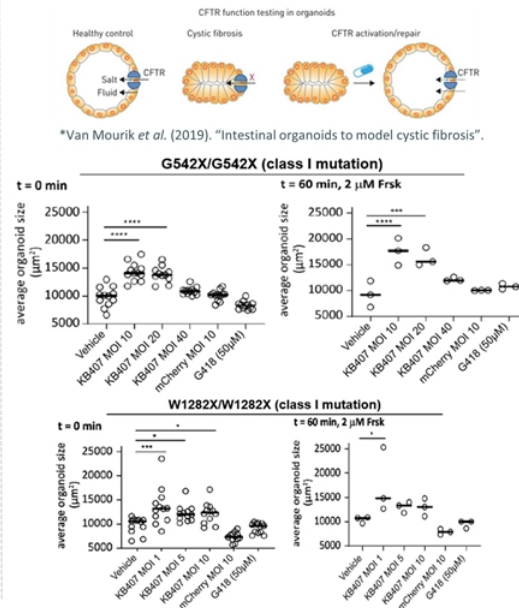


# Preclinical data supports KB407 in CF and broader development in lung disease

Robust, dose-dependent CFTR expression and functional correction in 2D airway epithelial cell culture

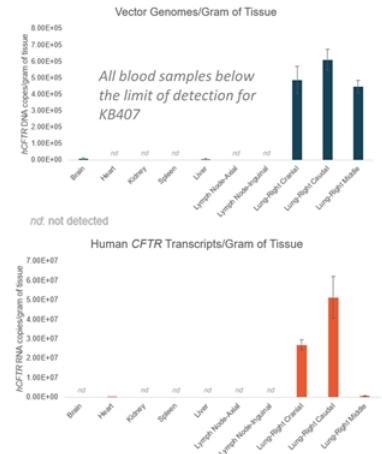


KB407-mediated functional correction of CF phenotype in clinically relevant 3D organotypic system (HUB)



Two repeat doses of KB407 in a nonhuman primate were well tolerated and distributed broadly throughout the lung

- No abnormal cage-side/clinical observations throughout study
- No gross findings noted at time of necropsy



# KB301 for aesthetic indications

KB301 and other discovery programs in Aesthetics, are housed in our wholly owned subsidiary, Jeune Aesthetics, Inc.

## KB301 aims to increase neocollagenesis, thereby correcting the underlying molecular defect of the aged phenotype

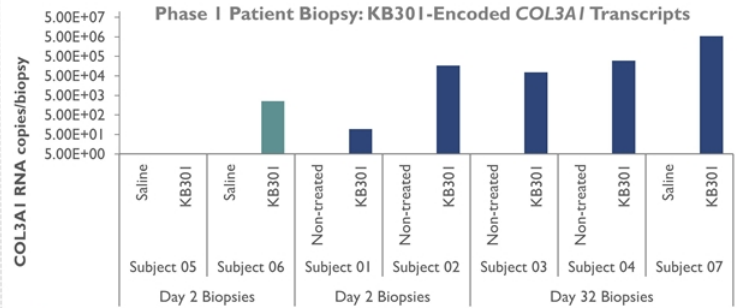
- Dermal collagen, composed primarily of types 1 and 3 collagen fibrils, represents >90% (dry weight) of human skin
- Declining levels of collagen are caused by reduced collagen biosynthesis and increased collagen fibril fragmentation resulting from both intrinsic (e.g., passage of time, genetics) and extrinsic (e.g., chronic light exposure, pollution) pressures
- KB301 is designed to deliver the gene for full-length type III collagen (COL3)
- It is injected directly into the area of interest, with the goal of targeted collagen production by the body's own cells

## KB301 is currently being evaluated in a Phase 1 trial (NCT04540900)

- The open label, dose ranging study will evaluate repeat dosing of KB301 injections
- Safety data from Cohort 1 (repeat KB301 injections into the buttock region) was reported at SID 2021
- Cohort 2 is currently enrolling and will evaluate efficacy of repeat doses of KB301 on the face and knees
  - ~30 subjects will be enrolled; bilateral treatment areas on the neck behind the ear, on the cheek below and above the zygomatic arch, and around the knee will be chosen and randomized 2:1 to receive low dose KB301, high dose KB301, or saline administered via in multiple micro depot injections over the selected treatment area
  - Change in skin quality from baseline will be assessed via the Skin Roughness Score (SRS), Fine Lines Score (FLS), and the Subject Satisfaction Score (SSS). Skin calipers will be used to measure the change in skin thickness over the knee

## Initial data from Cohort 1 of the Phase 1 study shows safety and tolerability of repeat KB301 injections

- Repeated intradermal injections of KB301 were well tolerated.
- Recorded adverse events were transient and limited to expected mild or moderate injection site or biopsy site reactions (e.g. erythema, site pain, purpura, ecchymosis)
- For all subjects who have completed follow up through day 90 (subjects 1-6; subject 7 follow up ongoing) no clinically significant changes in anti-drug antibodies were observed



- KB301-encoded COL3A1 expression measurable at the mid and high dose, with no detectable expression in control samples
- Expression was evident by day 2 following the first dose; expression levels were similar following the first and second dose

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# Financials and Milestones



# Krystal summary

*A fully integrated, clinical stage gene therapy company powered by proprietary HSV-1 vector technology*

## Current Status and Milestones

### Rare Skin

- **B-VEC:** Pivotal GEM-3 trial ongoing with topline data expected 4Q21. Commercial planning in US and EU underway
- **KB105:** Phase 2 study ongoing; Initiation of dosing in next Phase 2 cohort in 2022
- **KB104:** IND filing in 2022

### Jeune Aesthetics, Inc

- **KB301:** Phase 1 trial in aesthetic skin indications ongoing; initial Phase 1 efficacy data anticipated in 4Q21

### Rare Lung

- **KB407:** pre-IND work ongoing; clinical trial initiation anticipated in 3Q21

### Platform

- **Manufacturing:** Ancoris facility currently supplying all clinical material and will supply initial phase of B-VEC launch; Astra facility (150,000 sqft) construction underway, completion anticipated in 2022
- **Next Gen Tech:** Evaluation of novel effectors, routes of administration, and tissue tropism underway

## June 30, 2021 cash balance of \$389.1M

- B-VEC, KB105, KB104 and KB407 are PRV eligible



The Leader in Redosable Gene Therapy for Rare Disease

August 2021

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