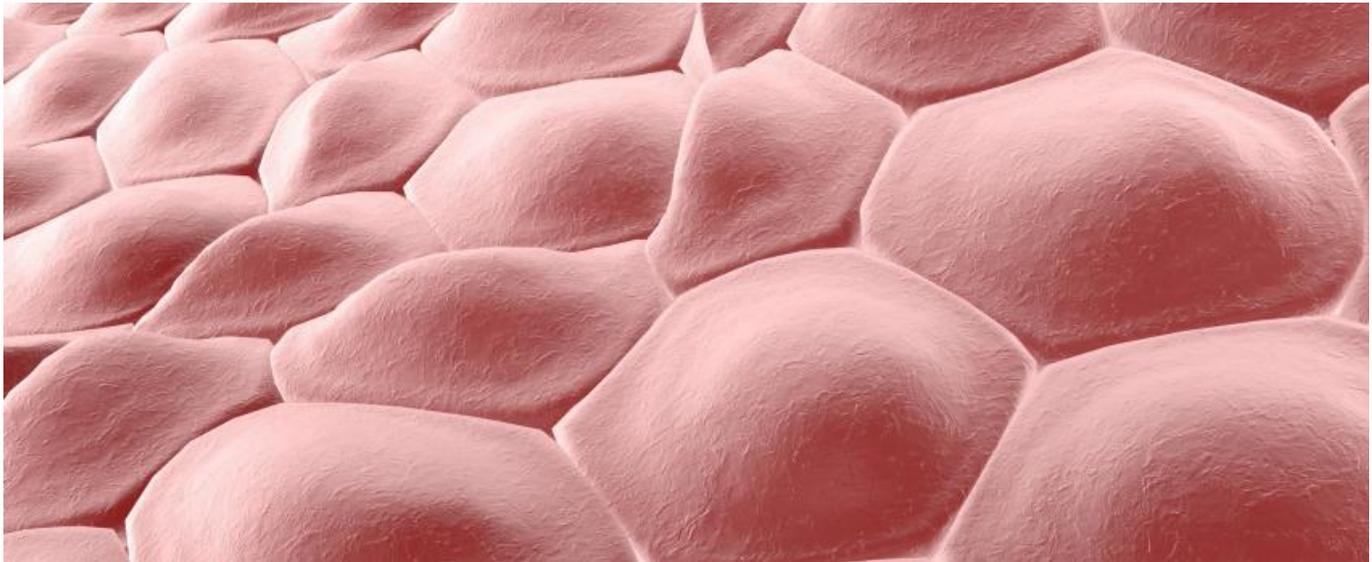


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Gene therapies go skin deep to tackle epidermolysis bullosa



[Madeleine Armstrong](#)



Three gene therapy contenders, Abeona, Fibrocell and Krystal, are taking different approaches in the quest to cure epidermolysis bullosa.

Gene therapies have provided hope to patients with various incurable diseases. And, after a long time with no options, those with the skin disorder epidermolysis bullosa have not one but three transformative treatments on the horizon.

With all three gene therapy players – Abeona Therapeutics, Fibrocell Science and Krystal Biotech – soon set to push into pivotal trials, the battle is heating up. Each company is taking a slightly different approach and, by next year, it should become clear whether one has an edge over the others.

EB patients have extremely fragile skin that is prone to extensive blistering. There is no cure for the disorder, and the only current option is wound and pain management.

An effective gene therapy would therefore be a game-changer. All of the aforementioned groups are initially taking aim at the dystrophic variety of the disease, caused by mutations in the *COL7A1* gene. Treatments that provide a functional copy of this gene are designed to spur the production of collagen VII, which holds the layers of the skin together.

But this is where the similarities between the three candidates end.

Selected epidermolysis bullosa projects in late & mid-stage development

Project	Company	Description	Status	Trial
AP101/ Episalvan	Amryt Pharma	Betulin formulated as topical gel	Phase III ongoing	Ease, NCT03068780
FCX-007	Fibrocell Science	Autologous, lentiviral vectored COL7A1 gene therapy	Phase III to start H1 2019	
EB-101	Abeona Therapeutics	Autologous, retroviral vectored COL7A1 gene therapy	Phase III to start mid-2019	
KB103	Krystal Biotech	Topical, HSV vectored COL7A1 gene therapy	Phase II	Gem-1, NCT03536143
QRX-313	Proqr Therapeutics	RNA-based oligonucleotide – skips exon 73 of COL7A1 gene	Phase I/II data due Q1 2019	Wings, NCT03605069
RGN-137	Lenus Therapeutics (Regenerx, G-treeBNT JV)	Tβ4-based dermal gel formulation	Phase II	NCT03578029
Diacerein	Castle Creek Pharmaceuticals	Diacerein formulated as topical gel	Phase II	NCT03154333 (terminated)

Source: EvaluatePharma, [clinicaltrials.gov](#).

The most unusual of the three is Krystal Biotech's KB103, an off-the-shelf topical gel that delivers COL7A1 via an attenuated herpes simplex virus ([Krystal gets more skin in the epidermolysis bullosa game, March 5, 2019](#)). Krystal is developing it for both recessive dystrophic EB, the more severe subtype, as well as the milder dominant form.

Abeona and Fibrocell, meanwhile, have taken more conventional gene therapy approaches with their autologous candidates, EB-101 and FCX-007 respectively. These both target recessive dystrophic EB.

Still, there are marked differences between the two projects. With EB-101 Abeona [uses a retroviral vector](#) to insert the gene into patients' keratinocytes. The end product is a skin graft – which [can take up to 27 days](#) to produce – that is surgically attached to the site of a patient's wound.

Meanwhile, Fibrocell uses a lentiviral vector to modify a patient's fibroblasts. These are then injected intradermally at the wound site during an out-patient procedure that involves conscious sedation – meaning that FCX-007 could be more patient friendly than EB-101.

In the first instance, producing FCX-007 takes around four months. However, once a bank of cells has been created for a given patient, they can be used repeatedly, Fibrocell's chief executive, John Maslowski, told *Vantage*.

"Patients have wounds all over their bodies, so physicians can treat the other areas with those banked cells," he said. "Once we've established a bank, injection two and beyond takes just a couple of weeks."

None of the EB gene therapy candidates is analogous to the systemic, once-and-done approaches that have so far dominated the gene therapy landscape. The need for several treatments for the same patient, but for different wounds, could make for interesting pricing conversations if any of them make it to market.

Durability

Mr Maslowski believes that FCX-007's effect might be more durable than the other candidates', saying: "We've seen data that our cells are lasting at least six months, and we suspect it's longer because we see wound healing out to a year." However, he conceded that even longer-term data are needed before Fibrocell can claim victory here.

One reason for the chief exec's confidence is that fibroblasts do not turn over as quickly as keratinocytes, which might give FCX-007 an edge over Abeona's EB-101.

Meanwhile, Krystal's KB103 targets both fibroblasts and keratinocytes. However, this project could be less durable anyway because of the transient nature of the herpes simplex viral vector used by Krystal – this does not integrate with the patient's DNA, so is eliminated when the transfected cells die.

Krystal's chief executive, Krish Krishnan, has told *Vantage* that this might not be an issue given that KB103, being a gel, could be reapplied relatively easily. But Fibrocell's Mr Maslowski argued that Krystal's approach might not be as simple as it seemed: "Because [KB103] uses a live virus, it would have to be administered on site. And travel is very difficult for EB patients." Thus, more frequent trips to the clinic could offset KB103's advantage on ease of application.

Mr Maslowski also contested Mr Krishnan's claim that all the EB gene therapy candidates would have a limited duration because of the natural turnover of the collagen VII fibrils. "Let's say the fibrils lasted several months and then disbanded – if the cells were still present they could reproduce the fibrils," he suggested.

First mover

Of course these considerations will only become important if all three projects succeed in phase III. Fibrocell looks to be the furthest ahead, with FCX-007 set to enter its pivotal trial in the first half of this year.

Meanwhile, the start of Abeona's phase III study of EB-101 has been pushed back from last year to mid-2019. The company has been busy establishing a GMP manufacturing facility for the project, which originated at Stanford University.

Krystal's KB103 is a little further behind: it is due to yield phase II data in the first half, and could go into pivotal trials by the end of this year.

There might be room for more than one EB gene therapy, Mr Maslowski believes. Fibrocell aims to treat smaller, earlier-stage wounds, with the chief exec admitting that Abeona's EB-101 would probably be more useful for larger wounds.

This stance was echoed by Abeona. A spokesperson told *Vantage* that the three approaches could be complementary, but added: "Only EB-101 has been shown in a robust dataset to safely treat larger wounds, with the potential to treat smaller wounds."

Mr Maslowski concluded: "Physicians tell us they're excited about all this activity, because they could get a lot of tools in the toolchest. There's room for a few products."

Other approaches in development include Proqr's exon-skipping project QRX-313 – due to yield clinical data imminently but only targeting patients with a certain mutation – and topical gels like Amryt's AP101.

With only around 1,000-2,500 patients in the US with recessive dystrophic EB, according to Fibrocell, subtle differences between the contenders could become important if more than one makes it to market.

This story has been updated to reflect the fact that EB-101 uses a retroviral vector.

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