Gene therapies go skin deep to tackle epidermolysis bullosa

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**

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

*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](https://www.vantage.com/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 intra-dermally at the wound site during an outpatient 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.