GENE EDITING: Overhyped or Unstoppable Tide?

BY MADELEINE ARMSTRONG | MAY 2023

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Introduction

A decade after Crispr made a splash as a possible therapeutic approach, the first product using Crispr/Cas9 gene editing is on the verge of approval. Vertex and Crispr Therapeutics' exa-cel has been filed with regulators, whose initial verdicts could emerge later this year.

Accompanying this breakneck speed of development are doubts about whether gene editing will ever become mainstream. The first gene editing wave consists of ex vivo projects that are cumbersome and unpleasant – patients' cells are first extracted and then a chemotherapy conditioning regimen administered to deplete the subject's remaining stem cells, before the edited cells are implanted. This approach is also extremely expensive.

To address at least some of these problems, companies are working on easier-to-administer projects that edit cells in vivo. However, this raises concerns about letting gene-editing machinery loose inside patients, and unintended consequences.

Worries about in vivo projects peaked last year with the FDA clinical hold for Verve Therapeutics' base-editing candidate VERVE-101, before it had even been near US patients.

This year's rapid green light for Intellia to start US clinical trials of its in vivo Crispr asset, NTLA-2002, calmed some of those jitters. But many remain sceptical about gene editing, particularly in diseases where there are already approved therapies, however imperfect.

When not if?

For this report, *Evaluate Vantage* spoke to various companies in the gene editing field, including those working on Crispr/Cas9 and the next big things, base-editing and prime editing. Also profiled are groups developing new delivery methods, a field that is getting increasing attention.

Despite the apparent regulatory caution, the mood among this cohort is predictably upbeat.

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"It's not a matter of if, it's when this becomes a dominant modality that changes the world," says David Hallal, chief executive officer of Elevatebio, whose Life Edit subsidiary inked a deal with Moderna in February.

He points to initial doubts about monoclonal antibodies, "and now they're the dominant modality within biotech and even big pharma". Mr Hallal believes failures will not just be surmountable, but necessary, to "learn from the mistakes along the way".

"I think some of the issues are just growing pains," says Keith Gottesdiener, chief executive of Prime Medicine, which managed a $175m IPO in 2022, the worst year for would-be public groups in recent memory. "We continue to see lots and lots of people who are excited about gene editing."

Akin Akinc, the chief exec of Aera, is a little more measured: "I'm quite confident that we have an upward trend line, but that path is probably not going to be smooth. That's just the reality of difficult science." That group launched in February with $193m in venture funding and a novel delivery technology based on research by the Crispr pioneer Feng Zhang.

Permanent change

The companies interviewed tend to agree, though, that the FDA's caution is warranted given the nature of the technology involved.

A spokesperson for Intellia describes the agency's standards as "appropriately high". However, the group does not buy into the idea that the FDA is stricter than other regulators, such as the EMA: "It has not been our experience that the FDA's requirements were somehow distinct or meaningfully different compared with other regulatory agencies."

"Gene editing is an area where I think regulatory bodies need to think carefully, because these are permanent edits to your genome," Prime's Gottesdiener says, while stressing the potential for an "incredible upside" in the form of a permanent cure.

Simon Harnest, chief investment officer at the private group Metagenomi, agrees: "We want to do this very cautiously because we don't want to salt the Earth with a rushed process."

Overall, the companies do not believe that in vivo editing is getting a tougher ride from regulators than ex vivo projects.

"It's anything new," says John Evans, chief executive of the base-editing specialist Beam Therapeutics. He highlights previous holds on gene therapies and even Vertex and Crispr's ex vivo-edited project exa-cel. "The difficulty is when there's something new, the FDA doesn't know exactly what to ask you for, because they don't know the science."

While some predict that in vivo editing will eclipse ex vivo technology, most of the companies interviewed believe there will be room for both. An exception is Ensoma, a private group focused on editing haematopoietic stem cells in vivo.

"I think the field is shifting to in vivo," says chief exec Emile Nuwaysir. "The ex vivo field has been a remarkable step forward and it's taught us a lot – but it's also taught us it's not practical."

If in vivo editing does make the leap into the mainstream, its impact on healthcare disparities could be akin to the effect cell phones have had on levelling the telecommunications playing field, says Gilmore O'Neill, the chief exec of Editas.

For this shift to happen, new delivery technology will be vital. Current in vivo therapies are mostly delivered using lipid nanoparticles (LNPs), which tend to head for the liver, therefore limiting use to liver-mediated disorders.

Adeno-associated viral vectors – already used in gene therapies – could provide an alternative outside the liver. These have drawbacks including their immunogenicity and long-lasting effects, however.

New delivery modalities are certainly on investors' radars. "For the first year of our existence, everyone tortured us on the editing," says Prime's Gottesdiener. "And over the course of that year, we convinced people we get very precise editing. And the minute that happened, they started torturing us on delivery."

With new editing technologies and delivery methods seemingly popping up all the time, the next few years could see a whittling down of the field as it becomes apparent which – if any – will succeed.

And as some of these cutting-edge therapies make it to market, questions about pricing and intellectual property are likely to become more prominent. For now, though, just getting some of these projects into the clinic will be a big step.

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Verve Holds Its Nerve

The gene editing world is full of tough tasks, but Verve Therapeutics has one of the toughest: convincing regulators – and doctors – that the world needs a base-editing therapy hitting PCSK9, the target of several approved injectable drugs.

The group's chief executive, Sekar Kathiresan, is used to addressing scepticism about Verve's mission. "I think it's underappreciated how much the unmet need is here," he tells *Evaluate Vantage*, noting that of all the heterozygous familial hypercholesterolemia patients in the world, only about 2% are at goal LDL cholesterol levels.

"The chronic care model – asking people to take a pill or injection for a whole life – just doesn't work." When asked about worries around the permanence of gene editing, he draws an analogy with surgical procedures that are also irreversible.

He is adamant that, if Verve can show the benefits of its project VERVE-101 outweigh its risks, "there'll be a lot of people who would be open to gene editing".

VERVE-101 is currently in a phase 1 study, Heart-1, which is recruiting patients in New Zealand and the UK. However, US progress stalled with November's FDA clinical hold on the company's IND application.

Kathiresan is reluctant to speculate on when this might be lifted, noting that the company is still talking to the regulator. But he does not believe the FDA's caution is around base-editing per se. "I don't think it's the technology. I think it has to do with the delivery," he says.

VERVE-101, which uses base-editing licensed from Beam Therapeutics, is delivered via LNPs. Intellia's NTLA-2002, which was recently cleared to start US trials, also uses LNPs – although that project is based on Crispr/Cas9 editing.

Intellia already has human data on NTLA-2002 from an ex-US trial, which might have helped smooth its path to US clinical trial patients. Beam's chief exec, John Evans, plays down the importance of those results, however. "The things the FDA is interested in are probably not things a little bit of phase 1 data would tell you."

Safety is the key endpoint, with Verve also measuring PCSK9 and LDL-C levels. Ultimately, the group wants to see a 60% and 40% reduction respectively, in line with Novartis's long-acting product Leqvio.

"We don't see any difference in the bar that the FDA is giving to base-editing versus nuclease editing", for example with Crispr/Cas9, he says. "If anything, we may have an easier path in some scenarios given our lack of double-stranded breaks."

There are concerns that double-stranded breaks, a feature of Crispr editing, could result in chromosomal abnormalities including translocations that could lead to cancer. Base-editing, meanwhile, merely nicks DNA and makes a single base change. It has been referred to as a "pencil" compared with Crispr's "scissors".

There are hopes that this precision could make base-editing safer, although the FDA is still taking a cautious stance and asked for more data on the risks of off-target editing with VERVE-101, among other things.

As well as providing preclinical data, Verve also expects to submit available results from Heart-1 in its reply to the FDA. Investors, meanwhile, will see data from the study in the second half of this year, once all four dose cohorts are complete.

Safety is the key endpoint, with Verve also measuring PCSK9 and LDL-C levels. Ultimately, the group wants to see a 60% and 40% reduction respectively, in line with Novartis's long-acting product Leqvio. "We want to get there at the end of phase 3. Whether we get there in phase 1, in the very first study for the very first application of new technology, we'll have to see," Kathiresan says.

In phase 1 "we just want to show that we can edit and deliver".

Beam: All About That Base

While Verve is squarely focused on in vivo editing, Beam is keeping its options open. “I do think there’s a home for ex vivo,” says chief executive, Evans. “There will be things you can do to cells ex vivo that you may never be able to do [in vivo].” With its allogeneic Car-T projects, for example, Beam aims to make “four or five or six edits. I don’t think that’s going to happen in vivo.”

Beam’s lead project is an ex vivo-edited therapy for sickle cell disease and beta-thalassaemia – the uses that Vertex and Crispr are targeting with exa-cel. The pipeline here was looking crowded until three projects dropped out in February – from Intellia/Novartis, Graphite and Sangamo – with competition looking a likely factor.

Evans is not perturbed about the prospect of coming late to a market that could already feature exa-cel and Bluebird’s sickle cell gene therapy lovo-cel.

“The assets that were deprioritised didn’t work that well. There’s absolutely room for better products. And we think that with base-editing, we’re going to deliver that with higher levels of editing,” he says.

This, in turn, could lead to higher levels of foetal haemoglobin; the aim of both exa-cel and BEAM-101 – as well as various other sickle cell projects – is to activate this form of haemoglobin to compensate for the effects of sickle haemoglobin. Exa-cel does this by reducing the expression of the transcription factor BCL11A. BEAM-101 is designed to increase gamma globin levels by mimicking mutations seen in people with hereditary persistence of foetal haemoglobin, who seem to be protected from sickle cell disease.

Trials have shown that exa-cel increases foetal haemoglobin levels to around 45% of total haemoglobin. Beam’s most recent corporate presentation raises the possibility of foetal haemoglobin levels of 65%, based on animal studies. This goal, which Evans calls “realistic”, will be tested in the phase 1/2 Beacon trial, which reads out next year.

Like other ex vivo projects, BEAM-101 involves chemo conditioning, but Beam is looking for a less toxic regimen to deplete stem cells.

Beam’s next wave of ex vivo sickle cell projects, dubbed Escape, will pair antibody-based conditioning with modified cells with two edits: one therapeutic and one designed to help the cells evade the antibody. “The antibody will clear away old cells, just like the others do, but it will leave our graft alone,” Evans explains.

Beam also has a pipeline of in vivo projects, mainly delivered via LNP and initially targeting the liver, where LNPs tend to accumulate. Eventually, the group hopes to develop in vivo projects for sickle cell, but here it will have to take its cargo to the bone marrow.

The group has so-called “barcoded” LNPs that it hopes to target to different organs, but it is keeping an open mind about delivery and is doing some early work on novel viruses and viral-like particles (more on efforts from other companies here later).

Beam has other editing irons in the fire. While it is known as a base-editing company, it also has a deal with Prime Medicine, giving it exclusive rights to develop prime editing in sickle cell.

The companies have close ties: they share a co-founder, David Liu, and as part of the aforementioned deal Beam provided interim leadership to Prime. The two technologies have a “similar feel”, Evans says, in that they are both built around Crispr/Cas9 to target the host DNA. With both projects, the Crispr protein is modified to nick, rather than cut, the DNA.

The effectors used are different, Evans explains: “In the case of base-editing, it’s a deaminase. In the case of prime editing, it’s a reverse transcriptase.” (More on how prime editing works later.)

The Prime deal looks like a way of making sure Beam will not be overtaken by prime editing in its therapy area of focus. “It pushes Prime Medicine to other indications that we’re not currently working on,” Evans says. “We also have prime editing as that evolves, if we want to use it.” That gives Beam “even more shots on goal”.

Ready For **Prime** Time

It is understandable that Beam does not want Prime on its turf. The way Prime's chief executive, Keith Gottesdiener, tells it, prime editing can reach the parts that other editing technologies cannot, with a limited risk of off-target editing.

The company has a long way to go to prove this in humans, though. Despite floating last year, Prime does not expect to file its first IND until 2024 – likely for its ex vivo project for chronic granulomatous disease.

Gottesdiener contends that this is a fast timeline, given Prime was only formed in 2020. The group's early nature clearly did not dissuade investors, who helped Prime to the fourth biggest flotation of 2022.

Being behind other gene editing companies might not be all bad, the chief exec says. "I would love it if we were the clinic today. But the advantage is, we get to see what other companies have done. Not just from a regulatory perspective – we get to see some of their scientific approaches."

Ultimately, though, Prime hopes to set itself apart from the competition. The group claims that prime editing is the only modality with the ability to edit, correct, insert and delete.

Crucially, it avoids the double-stranded breaks that Crispr/Cas9 editing creates. "Double-stranded breaks are really an emergency signal to the chromosome, you're basically breaking it. And the cellular machinery just fills it in with whatever it can," Gottesdiener says.

"That's great if you want to inactivate a gene – it's what Crispr does best. But it is an uncontrolled process."

Base-editing also avoids double-stranded breaks, but prime editing can do "lots and lots more things," Gottesdiener says. "Just to put it in context, base-editing can fix four nucleotide mismatches out of 12 possible ones – we can fix what base-editing does as well as the other eight." Prime editing can also insert and delete DNA sequences.

He points to early work on "looping out" large amounts of DNA – which could be useful in repeat expansion diseases like Huntington's – and inserting large stretches of DNA. The latter is a big goal for the gene editing field.

When it comes to inserting, prime editing's precision will be key, according to Gottesdiener. "People can put a lot of DNA into the genome today, that's what a lentivirus does. The difference is, can you put it into a very specific location?"

This specificity comes from prime editing's three-stage process. "It's like having a door with three keys: if you don't open all three keys, you can't get into the house. We can't do the edit until all three of those matches occur. And the chance that all three of those matches are going to occur at the wrong site starts to become incredibly low."

A prime editor incorporates a modified Crispr/Cas domain – usually Cas9 – and a reverse transcriptase domain. The former targets and nicks the host DNA, while the latter writes a new DNA sequence into the host's genome – using a template from a third component, pegRNA.

This pegRNA contains both a "search" and "replace" sequence; the search sequence is the first "key". Once this matches with the DNA target, Crispr/Cas9 nicks the host DNA, creating a single-stranded RNA flap.

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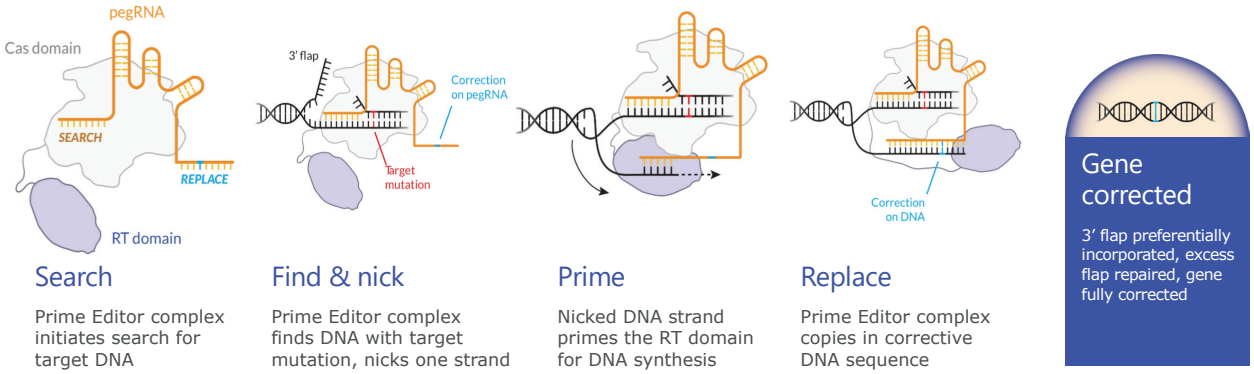
This flap binds to a region of the replace sequence – the second "key" – triggering the reverse transcriptase to write the new, corrected code into the host's gene.

"And when we're done, you need to be able to then match a third place in order to put it all back together again," Gottesdiener says.

Figure 1. How Prime Editing Works: Programmable for both search and replace



Search
Prime Editor complex initiates search for target DNA

Find & nick
Prime Editor complex finds DNA with target mutation, nicks one strand

Prime
Nicked DNA strand primes the RT domain for DNA synthesis

Replace
Prime Editor complex copies in corrective DNA sequence

Prime is looking at ex vivo and in vivo projects, and delivery via both LNPs and AAVs. The latter is being reserved for settings "where there are no alternatives", says Gottesdiener. "For example, you can get to certain brain structures with AAV. We're not going to wait for a perfect solution. We'll work with AAVs [until] better delivery methods come along."

Prime already has 18 programmes in development, albeit at a very early stage. Given the potential of prime editing, there are a lot of other possible applications. "We have probably close to another 100 places that we've at least seriously considered working."

The company cannot take on 100 diseases itself, and Gottesdiener says it is "talking to partners pretty much every day".

He concedes that Prime has a lot to prove, but is clearly excited: "I joke that I've drunk the Kool-Aid on this. I really, really think this is going to work. But I'll feel better when we can show people the data to support it."

Life Edit: Any Edit, Anywhere

Prime is not the only one trying to push the boundaries of gene editing. The private company Elevatebio, through its subsidiary Life Edit Therapeutics, makes the bold claim of being able to make "any edit, anywhere".

However, this group looks even further behind – Elevatebio's chief exec, David Hallal, says it is too early to say when the group might get an editing project into the clinic, or even which disease areas it is working in.

While the likes of Intellia, Beam and Prime are focusing largely on one editing technology, Life Edit is looking at various modalities with the aim of offering "a full range of gene-editing systems", Hallal says.

Underpinning this approach is "a really diverse set" of RNA-guided nucleases, says Clare Murray, senior vice-president of corporate development and operations at Life Edit. The company has close to 100 nucleases, she adds, sourced from a "proprietary collection of microbes" originally developed by Agbiome, the crop protection specialist Life Edit was spun out of in 2020.

She also highlights a range of Pam motifs, short sequences that are important for targeting the gene-editing machinery. Overall, this "allows us to go anywhere we want to in the DNA to do the editing we want to do", she says.

As well as nucleases, Life Edit is also looking at deaminases for base-editing, and reverse transcriptase editing, analogous to prime editing.

In February, the company received validation in the form of a deal with Moderna, albeit for an undisclosed fee. The larger group called out base-editing as an area of particular interest. "While we're not disclosing therapeutic areas or disease targets they highlighted, as you might imagine with mRNA and LNPs, they'd love to target the liver with our combined technology," Hallal says.

Life Edit is developing both in vivo and ex vivo approaches – and in the latter it plans to harness the cell therapy expertise of its parent company. Murray believes there will still be room for more collaborations. "We believe that we can build a robust pipeline internally across Life Edit and Elevatebio, and still have plenty of opportunity to partner."

As for delivery, Life Edit is looking at both viral and non-viral approaches. "We want as many options on delivery as we have on editing," Murray says.

The group is also developing small nucleases, which could be particularly important for delivery via AAV vectors, as these have a limit on the size of the cargo they can carry.

As well as nucleases, Life Edit is also looking at deaminases for base-editing, and reverse transcriptase editing, analogous to prime editing.

Metagenomi: A 20,000-Nuclease Library

Life Edit is not the only group taking a broad approach. Another is Metagenomi, which also has a collaboration with Moderna, dating back to late 2021, as well as a deal with Ionis, inked last year.

The privately held developer has other similarities to Life Edit: it also boasts of a large library of gene-editing systems and a diverse set of Pam sequences. Metagenomi is ahead, however, with its lead asset set to hit the clinic in 2024. This is a Moderna-partnered in vivo project based on nuclease editing for an unnamed liver disease.

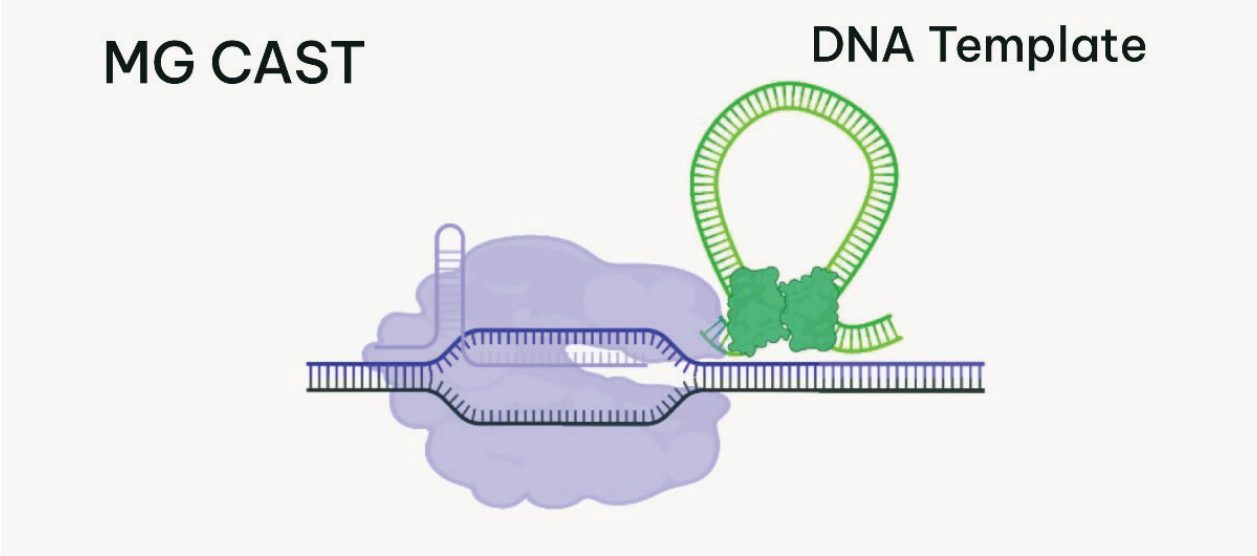
Metagenomi and Moderna's tie-up is unaffected by the big biotech's agreement with Life Edit, Simon Harnest, Metagenomi's chief investment officer, says. "I think we were smart in our alliance with Moderna to keep our target list to a certain limit, because we didn't want to give up everything to Moderna. So it's only natural that Moderna would partner with other companies."

"But Moderna is also growing its Moderna Genomics platform, and I think they are growing it because they're excited about what they see from us," he says.

Still, the mystery Metagenomi-Moderna asset is really just designed to show proof of concept, Harnest says. "It's actually quite the outlier. The rest of the technologies we're working on [do not make] double stranded breaks."

As well as nucleases, Metagenomi is developing assets for base-editing, prime editing, and Crispr-associated transposases (Casts). The last two could enable large gene corrections. While prime editing relies on RNA as a template, Casts could allow the insertion of large chunks of DNA, something Harnest describes as the "Holy Grail".

Figure 2. Casts



Simon Harnest is secretive about the projects the company is pursuing with Casts, but says the approach could have potential in diseases involving large genes, such as haemophilia A and cystic fibrosis.

Like Crispr nucleases, Casts occur naturally in bacteria, Harnest says. “The trick is to make them work in human cells.” Regarding intellectual property, Metagenomi is “filing aggressively” in a process started last year.

The exec is secretive about the projects the company is pursuing with Casts, but says the approach could have potential in diseases involving large genes, such as haemophilia A and cystic fibrosis.

Metagenomi finds its gene-editing tools by using artificial intelligence to analyse soil samples – Harnest declines to comment further on the group’s sources. From this work, it has identified around 20,000 potential editing systems, “and we’ve sorted through maybe 100 of those”, he says, stressing that the group does not use technology invented by anyone else.

The company has said it plans to advance only nucleases that are equal to or better than Cas9. But what does this mean in practice? Broad targeting is key to the group’s efforts, Harnest says. “Crispr/Cas9 has one Pam sequence. And we believe that this one Pam sequence as a targeting mechanism is not the optimal one for all gene targets.”

Pams are important to help the gene-editing machinery home in on the target area within the genome. “If you only have one Pam sequence, the further away you get from that Pam sequence to find the target, the more potential wobbling or off-target effects you’re going to get,” Harnest says.

Conversely, “If you have a series of nucleases with different Pam sequences, you can use one that has a Pam sequence in closer proximity to the target site. We believe that’s what achieves higher editing efficiency and less off-target effect.”

“I think people are opening up their minds to the fact that gene editing is not one screwdriver or one hammer, but you need a full toolbox,” he says.

Even if he is right, Metagenomi is well behind the gene editing leaders. Like Prime’s Gottesdiener, Harnest doesn’t think this is necessarily a bad thing. “Sometimes it’s good not to be first, especially when it comes to regulatory questions for a completely new technology. By the time we go into the clinic in 2024, we will have more knowledge, and we can use those blueprints and follow quickly.”

As well as its editing technology, Metagenomi is also working on non-viral delivery technologies beyond LNPs, but Harnest declines to elaborate. One question is whether, with so much going on, the group risks spreading itself too thinly – something he acknowledges. “We try to stack our programmes in a way that we don’t have to do everything ourselves,” he says.

Investors do not seem too worried on this front. In January the group carried out a $100m series B extension, taking the total raised in the round to $275m.

Aera: Time To Deliver

One company that has more to say on the question of delivery is Aera Therapeutics, which was launched in February with $193m in venture funding. The large sum is not the only reason Aera made a splash – it counts the Crispr pioneer Feng Zhang as founder and uses technology based on his research.

Investors were attracted by the prospect of improving the delivery of advanced therapies, a topic that has come to the fore relatively recently, Aera's chief executive, Akin Akinc, says. "Maybe 10 years ago there was a lot of focus on the payloads, and delivery was this underappreciated thing that people assumed you'd be able to just sort out."

The former Alnylam executive points to the "amazing modalities" that have been developed, from RNAi to gene therapy, and now gene editing. "But the reality is, the advancement of delivery technologies has lagged. If you look at pipelines today, it's still a lot of ex vivo and a lot of in vivo in the liver. People are recognising we really need new delivery approaches so we can unlock the full potential of what these modalities can achieve."

Aera's technology is based on so-called protein nanoparticle (PNPs): endogenous human proteins "that have had an ancient evolutionary origin from retroelements, like retroviruses. Meaning that they still have the ability to form capsid-like structures, encapsulate and transfer nucleic acid cargo, but the body has co-opted them to do different functions," Akinc says.

Using human proteins could have advantages over delivery systems based on viruses, he says, including reduced immunogenic risk. This could lead to improved safety and the ability to redose.

There are around 85 such proteins in the human body, according to the chief executive, and the size of the structures they form can differ. "Some of them are going to have different packaging limitations. We have members that can carry large cargoes like gene-editing cargoes, but we might have others that are better for small cargoes like siRNAs or antisense oligos. So I think it's quite flexible in that regard."

Aera's technology, therefore, could be used to deliver a wide range of advanced therapies, not just gene editing, which raises questions about how the group will prioritise its work. "There's no way we're going to be able to do everything on our own. I think partnership is in our future," Akinc says, though the money Aera has raised means it is in no rush to do a deal, he adds.

Investors were attracted by the prospect of improving the delivery of advanced therapies, a topic that has come to the fore relatively recently.

The company is also developing its own gene-editing technology, based on a new family of editing enzymes called the IscB proteins. "They appear to be the ancestors of Cas9 – they have all of the functional attributes of Cas9, but they're about a third of the size," he says. This means they could be easier to package up and deliver, like other small editing systems such as those being developed by the likes of Mammoth Biosciences.

While the IscBs themselves make double-stranded breaks, they could also be used as a platform for base or prime editing systems, in the same way that Cas9 has been used as a building block.

"Ultimately, we want to be a genetic medicines company that moves its own drugs and pipeline forward, in addition to enabling others," Akinc says.

As for Aera's focus, it is too soon to give firm details: "We're really interested in things outside the liver. Or if we can take applications that are currently ex vivo and move them in vivo," he says. In other words: "Where are we solving a problem?"

He acknowledges that the company's work is early – both on the gene editing and delivery side – but says investors recognise this. "[There's] an appreciation for how difficult this problem is. This isn't going to be solved really quickly with a limited amount of resources."

Ensoma: Hitting Haematopoeitic Stem Cells

Another private group, Ensoma, is taking a different approach. The company claims to be the first to deliver in vivo editing to haematopoietic stem cells, and it does this using virus-like particles.

Current in vivo therapies are limited to liver-mediated disorders, while diseases of the blood, such as sickle cell disease, can currently only be treated by ex vivo approaches. Ex vivo approaches are "not practical", says Ensoma's chief executive, Emile Nuwaysir. "We're only going to cure people that have access to the best hospitals in the world."

Targeting the haematopoietic stem cell in vivo is the answer, he says. "It's the source of your entire blood and immune system. Also, the blood system contacts every organ and cell in your body at every moment of your life. So if you wanted to deliver something therapeutic, what better way to deliver it than with the blood system?"

As well as genetic disorders, the company is taking aim at cancer, for example by engineering a patient's own T cells to attack tumours. The group also signed a deal with Takeda in early 2021 covering up to five unnamed rare diseases. However, the future of this work looks uncertain after the Japanese group said in April that it was stopping early research into AAV vector-based gene therapy and rare haematology. Nuwaysir says Ensoma is still evaluating how the news will affect its programmes.

Ensoma's delivery technology is based on virus-like particles, with the viral genome completely removed to help minimise a patient's immune response to the vector.

The system also has a payload capacity of 35kb, more than seven times the limit of AAVs, the company says. This could be particularly useful for inserting large payloads like Car constructs for oncology, Nuwaysir says.

As for how the vector is targeted to the haematopoietic stem cells, he explains that this comes from "a combination of engineering the capsid with different serotypes of adenovirus, and then introducing point mutations to make it more specific for the haematopoietic stem cell".

As with Aera's approach, the intention for Ensoma's vector is to deliver a range of payloads. One of these has come via the group's January acquisition of Twelve Bio, which had developed a nuclease based on Crispr/Cas12a.

Cas12a is smaller and more specific than Cas9, and the group's technology is designed to make multiple edits simultaneously. "It's unique to the Cas12a that we're using," says Nuwaysir. "It's harder to do that with Cas9." This multiplex editing could come into its own with Ensoma's Car-T projects, with edits "designed to improve function and promote expansion, stemness, persistence, and resistance to exhaustion".

Another aspect of Ensoma's vector, which it says is unique, is the claim to be able to make the effects of editing transient, permanent, or anything in between, using transposase machinery encoded within the VLP. "By altering the position of the transposase recognition sites in the construct – which tell the transposase which DNA to grab and insert – we can control which segments of the construct are inserted, and therefore permanent, and which are expressed transiently," he says.

Most other vectors "are either all one or the other", he says: AAVs are all "pretty much episomal", meaning they exist as a separate entity to the host genome and are therefore transient, while lentiviruses are integrating and therefore permanent.

Of course, Ensoma still has much to prove, and with Nuwaysir not saying when the technology might enter the clinic, the group looks a long way from proving it.

The company claims to be the first to deliver in vivo editing to haematopoietic stem cells, and it does this using virus-like particles.

Editas Targets A Comeback

One gene editing name that has had a rough ride of late is Editas, but the group still believes it has something to offer. At the beginning of the year the company abandoned its lead in vivo-editing projects following disappointing results in a rare eye disease, and sold its induced pluripotent stem cell-derived natural killer cell programmes to Shoreline Biosciences.

The current focus for the group, which has been through several chief executives in recent years and is currently headed by Gilmore O'Neill, is the ex vivo-edited project EDIT-301 for sickle cell disease and thalassaemia.

Earlier-stage in vivo assets are also in the works, with Editas also hoping to target haematopoietic stem cells. The group is looking at "a number" of potential delivery vehicles, including lipid nanoparticles, O'Neill says.

He declines to give more details on how these might work. "There's elements of the technologies that we need to continue to work on from the targeting point of view," he says.

The group's lead in vivo project will also be in sickle cell disease and thalassaemia, but O'Neill will not be drawn on when it might hit the clinic. Beyond this, Editas is interested in other targets, both liver and non-liver, but these are still top secret.

As well as targeting haematopoietic stem cells, Editas has other things in common with Ensoma: both groups are using versions of Crispr/Cas12. O'Neill says that the two companies' enzymes are engineered differently, but professes to be "delighted" that Ensoma sees potential with this approach.

O'Neill points to improved accuracy and potency with Cas12a which, he believes, should make EDIT-301 relevant – even though it is well behind Crispr and Vertex's exa-cel in terms of development.

He also reckons Editas has a better approach in targeting the promoter regions of the gamma globin genes to mimic the effect of hereditary persistence of foetal haemoglobin.

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Exa-cel boosts foetal haemoglobin by reducing the expression of the transcription factor BCL11A.

O'Neill contends that editing gamma globin leads to better red blood cell health than editing BCL11A. The hope is that this promotes better outcomes in patients – but this will need proving in the clinic.

So far, Editas has released foetal haemoglobin data on one patient, which looked in line with results with exa-cel. More data from the Ruby trial of EDIT-301 are due mid-year, but it is unclear how many patients this update will involve.

O'Neill is not worried about being late to a market that could also feature Bluebird's gene therapy lovo-cel, pointing to the potential for differentiation. He also believes that the "vast majority of patients will still be waiting for therapy at the time of our approval", because of various factors including an adjustment of stem cell therapy sites to a commercial model, and initial hesitancy from payers.

He points to the recent example of Car-T, which began with very slow uptake.

He is also unconcerned about the prospect of competition from Beam, which as previously outlined is also targeting gamma globin with BEAM-101. "I'd be delighted to see their data when they show it," he says.

Ultimately, O'Neill says that more choices would be good for patients. However, an in vivo therapy for sickle cell disease could change the landscape, making ex vivo options a lot less appealing. Editas will have to hope it does not get left behind again.

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