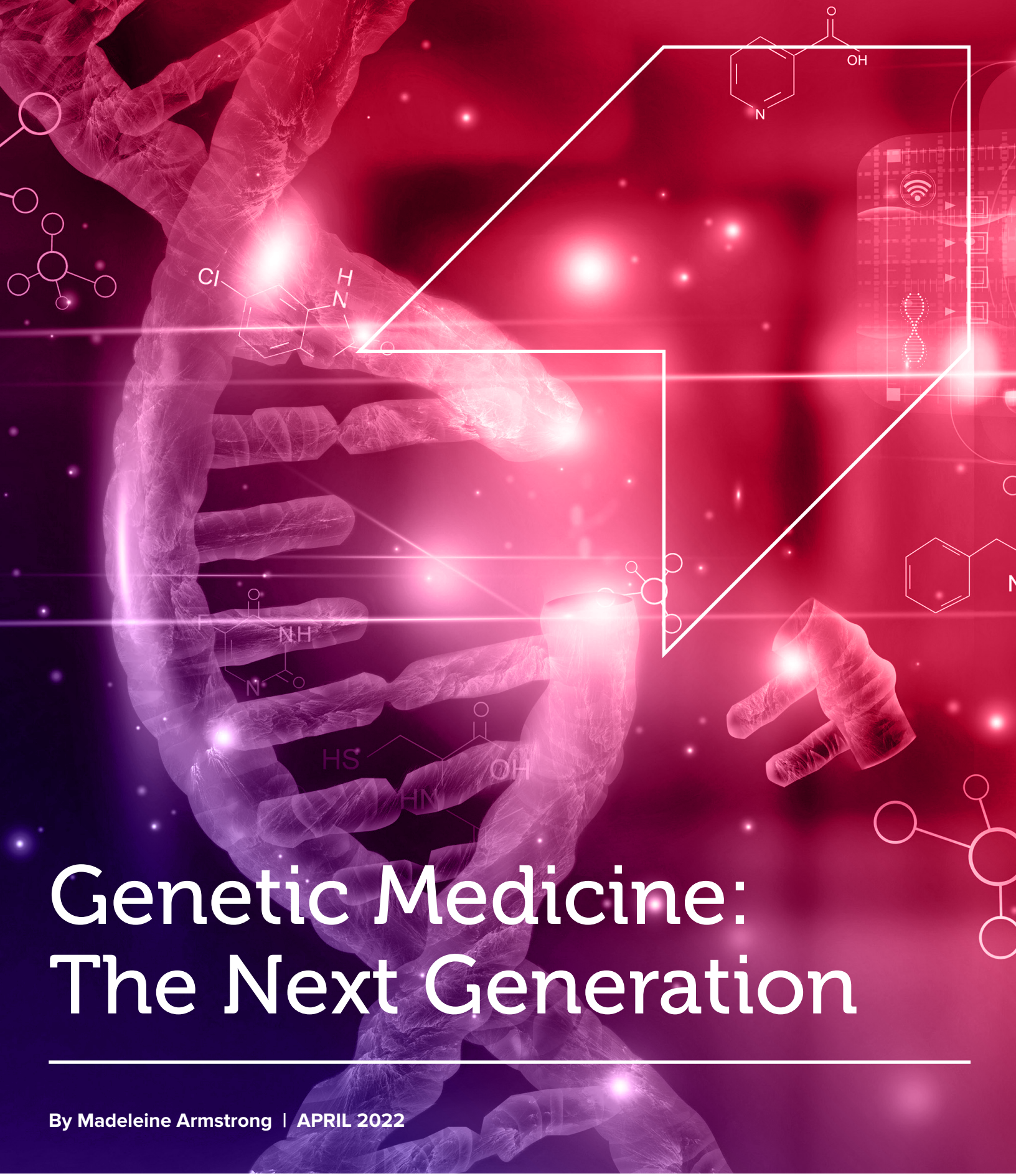

Genetic Medicine: The Next Generation

By Madeleine Armstrong | APRIL 2022

Evaluate Vantage

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Introduction

Once upon a time, a gene therapy player could release data on a handful of subjects and see its share price rocket. The sector was riding high after the landmark approvals of Luxturna and Zolgensma, and big pharma was keen to buy into this space. Valuations surged as investors clamoured for a piece of the pie.

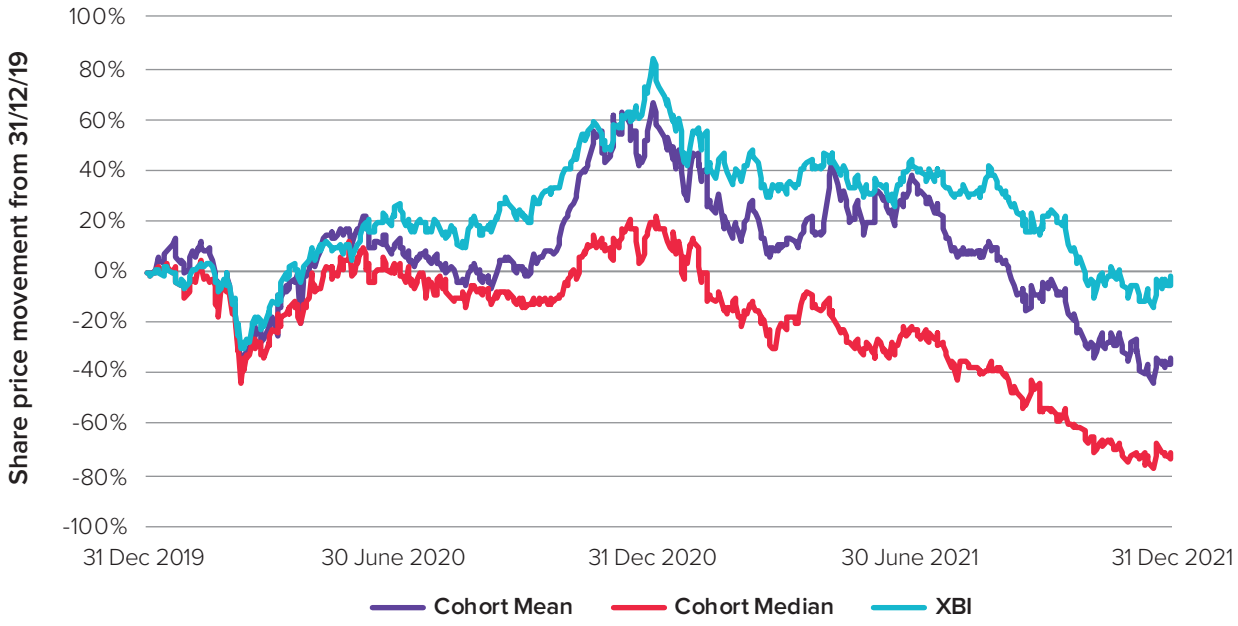
Those days are long gone. The US biotech bear market has been particularly tough on gene therapy and editing groups, whose multi-billion-dollar valuations always looked rich considering that the technologies involved were mostly unproven.

The field has had other issues to contend with, too. Top of the list are growing worries about toxicity and lack of durability.

“Things started popping up, one after the other, that started making people wonder: is gene therapy a little bit overhyped?” the Stifel analyst Dae Gon Ha, who covers a range of gene therapy and editing companies, tells *Evaluate Vantage*.

The chart below, which includes a cohort of 35 gene therapy and editing companies, shows just how hard the sector’s fall from grace has been.

The rise and fall of genetic medicine stocks



Note: Cohort comprised of 35 listed biotechs with a primary focus on genetic medicines

Mr Ha cites **patient deaths with Astellas's X-linked myotubular myopathy project** AT132, and a spate of clinical holds over the past couple of years. One particularly worrying aspect for shareholders, the analyst says, is that some projects are going on hold based on preclinical findings.

Regulators' caution seems justified. Looming large over the sector is the risk of insertional mutagenesis, namely the possibility that integration of a gene into the host genome could cause unwanted changes and lead to cancer.

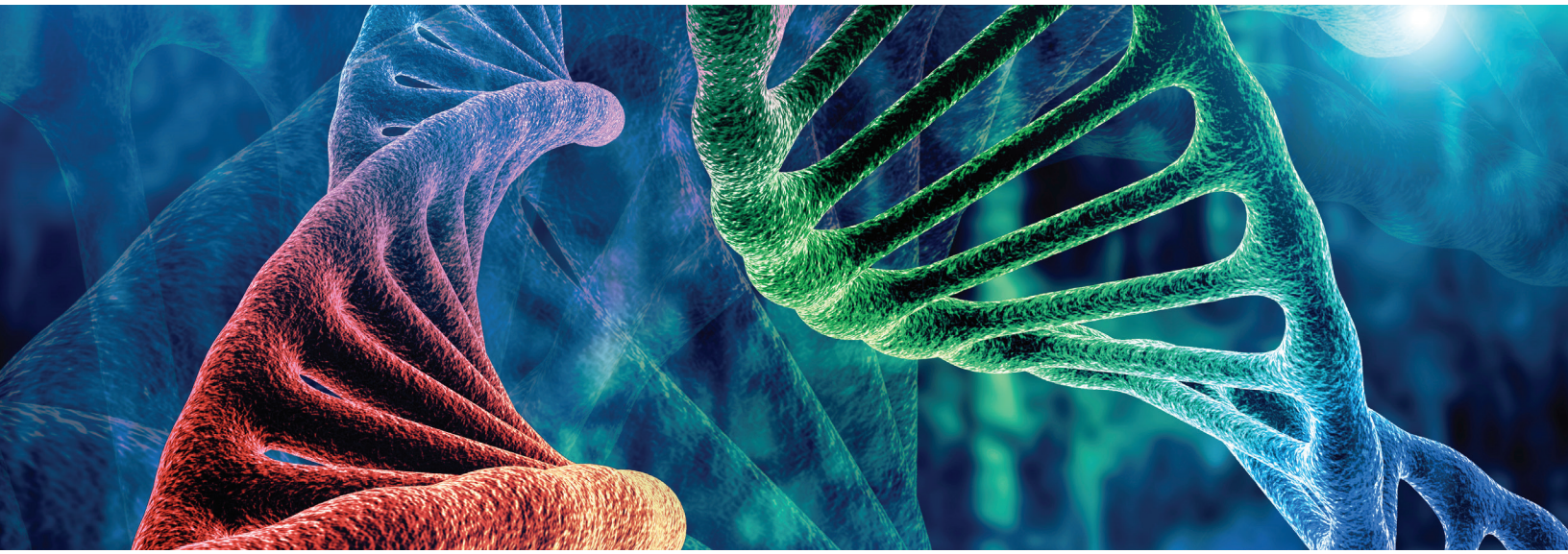
On the gene editing side, Crispr/Cas9 technology comes with its own worries about double-stranded breaks and resulting chromosomal changes.

These risks remain theoretical, however, and recent gene therapy cancer scares **have come to nothing**. Perhaps more pressing are concerns over liver toxicity, which **has been seen with particularly high doses of gene therapies** that employ adeno-associated viruses (AAVs) as vectors – currently the most common delivery vehicle.

One problem with current gene therapies is their narrow therapeutic window, and companies have recently grabbed attention – **and big pharma deals** – by developing more targeted vectors that could allow lower dosing and therefore avoid toxicity.

Still, even mild liver enzyme elevations could cause problems in the real world, Mr Ha says. Gene therapy patients are often given steroids – either prophylactic or reactive – to manage these liver enzyme rises, which are part of the body's immune reaction to the viral vector. The impact of these drugs on patients is often overlooked, the analyst says, and he questions how acceptable strict immunosuppressive regimens will be to patients.

All of this means that the risk-benefit equation for the current generation of genetic medicines is heavily skewed towards rare, life-threatening diseases for which no therapies are available. In less severe disorders, "even the remote possibility of an integration risk could come under the spotlight", Mr Ha says.



Durability and pricing

Then there is the question of durability. AAVs prime the immune system to attack upon subsequent detection, meaning that therapies using these vectors can only be given once.

Gene therapy proponents have made much of the “once-and-done” promise, but the fact remains that, if you only have one shot, you need to make it a good one.

In some cases, initially encouraging results have faded, leading to questions about how long any treatment effect might last. This issue could end up derailing a gene therapy contender that was once considered one of the most promising: Biomarin’s haemophilia A project valrox.

If gene therapies are not true cures, it will be difficult to justify million-dollar price tags. Indeed, high prices have already led to pushback; notably, Bluebird Bio pulled out of Europe last year after failing to strike deals with payers there.

This issue will come into particularly sharp focus for gene therapies and gene-edited projects that are being developed for disorders that primarily affect people in poor nations, such as sickle cell disease. Even in the US **there are questions about whether patients will be able to access them**.

Manufacturing complexities do not just mean a high cost: **there are fears that the quantities of AAV vectors needed to treat patients at scale could be untenable**. And the FDA has been keen to see consistency across the eventual commercial-grade product, slowing the progress of some gene therapy groups.

However, various players are working on technologies that aim to address the issues outlined above – some of which are profiled in this report. All the companies interviewed are doing something different: from non-viral delivery with lipid nanoparticles and scaffolds, to base editing for common diseases, to Crispr/Cas9 to treat infectious diseases, to perhaps the most ambitious idea of all: gene coding.

All of these approaches are very early and have a lot to prove. Progress is desperately needed to rebuild investor support in this field.

The lipid nanoparticle generation

One way of addressing concerns with the current generation of gene therapy is by using a different delivery method. This is the approach being taken by Generation Bio, which is harnessing lipid nanoparticles – the same method that has been used to deliver mRNA vaccines for Covid.

The group's vision initially garnered fans, and Generation carried out a $230m IPO in 2020 despite having no projects in the clinic. However, things have not gone smoothly since. The company's stock plunged in December after it disclosed that promising mouse data with its haemophilia A project **had not translated to primates**.

> "Nothing's gone wrong. The translation from mouse to non-human primate is the central challenge to developing a LNP delivery system. And we're at a mid-point in that process."
>
> **Geoff McDonough, Generation's chief executive**

Generation's chief executive, Geoff McDonough, insists that this was not a setback but just a normal part of cutting-edge drug development.

"Nothing's gone wrong," he tells *Evaluate Vantage*. "The translation from mouse to non-human primate is the central challenge to developing a LNP delivery system. And we're at a mid-point in that process."

Public vs private

Generation is now worth a quarter of what it was when it floated, but the chief exec insists that he has no regrets about going public. Mr McDonough reckons that building the necessary scale as a private company would have been tough. "And after having made that trade, you do ride the waves. But no one ever got to be a great sailor by sailing on calm seas."

If Generation can navigate these choppy waters, the company's potential is "hard to describe or imagine", Mr McDonough says. The company hopes to take gene therapy from its current niche in rare disorders to a mainstream, more drug-like treatment that can be redosed.

The use of LNPs is key to this aim. For one, "LNPs are not going to generate the immune response that a viral capsid would," Stifel's Mr Ha says.

The ability to redose means that a therapy can be better tailored to individual patients. This could also help prevent over-dosing patients, thereby reducing the potential for toxicity. Also, if the effect of therapy did begin to wane, it could be given periodically.

Another advantage of LNPs is that they can carry a larger cargo than AAVs, opening gene therapy up to disorders in which a large gene is affected. Generation has projects in Stargardt disease and Leber's congenital amaurosis 10, which involve genes that are too large for AAV capsids.

The potential for insertional mutagenesis will also be an important consideration. Generation believes that its approach, which involves the delivery of close-ended DNA (ceDNA) to the nucleus of a target cell, should minimise this risk. ceDNA is already double stranded and has no free ends, reducing the possibility of integration, Mr McDonough says.

Obviously, this all needs to be borne out.

Generation's main focus is on diseases of the liver, the easiest organ to target with LNPs. But it also has ambitions to direct its LNPs elsewhere, with several projects in eye disorders and plans to go into muscle and the brain.

Competition

Direct peers of Generation are hard to find, but the Swiss group Anjarium, which **raised a €55m series A round last September**, looks to be doing something similar. Anjarium declined to be interviewed for this report.

Code Bio is also taking a non-viral approach, but is eschewing LNPs and instead has created its own DNA scaffold for delivery of a genetic payload; more on this later.

Others are using LNPs to deliver gene-editing therapies, including the Crispr/Cas9 specialist Intellia, whose in vivo project NTLA-2001 **yielded first-in-human data last year**. Crispr Therapeutics **also has LNP projects**, while others are using this delivery route for more precise base editing, including Beam Therapeutics – **which recently signed a deal with Pfizer** – and Verve Therapeutics.

> "As the cells multiply, the therapeutic DNA does not undergo replication, so it gets diluted. Theoretically, you'll lose efficacy over time."
>
> **Dae Gon Ha, Stifel analyst**

Generation's Mr McDonough believes that the gene-editing approach has limitations. "All RNA-based technologies today are limited to either making finite base editing changes, or relatively small stretches of DNA. For large genetic disease categories, it's not so common that you have only one base change that accounts for the whole population," he says.

Gene therapy allows the delivery of a whole gene. However, AAV-based therapies are considered less durable than gene editing as, once they deliver a gene to a cell, it exists as a separate entity to the host genome. As Stifel's Mr Ha explains: "As the cells multiply, the therapeutic DNA does not undergo replication, so it gets diluted. Theoretically, you'll lose efficacy over time."

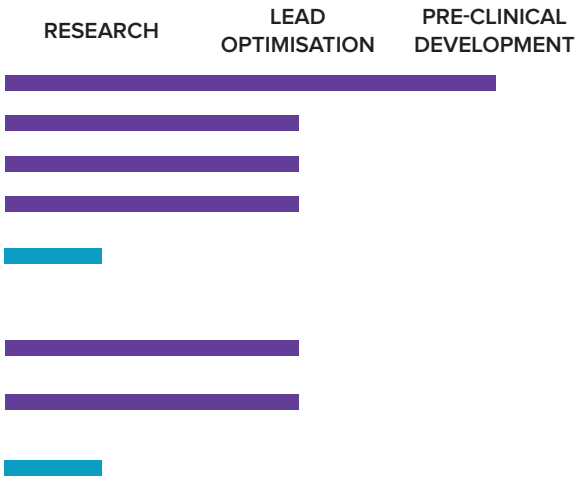
The private group Saliogen hopes that its so-called “gene coding” approach could represent the best of both worlds: it says its technology could allow the insertion of DNA of any size into the host genome. That company is also profiled below.

Mr McDonough says Generation is also working on delivering ceDNA into patients’ chromosomes – however, this work is even earlier than its core programme.

The company previously said it hoped to take its haemophilia A asset into humans in late 2022 or early 2023, but it is no longer giving guidance on timelines. It has plenty of cash for now – enough to take it into 2024 – but Generation has a lot to do to win back investors.

Generation Bio’s pipeline

TISSUE	PREVALENCE	INDICATION
LIVER	Rare diseases	Haemophilia A
		Phenylketonuria
		Wilson disease
		Gaucher disease
	Prevalent diseases	Endogenous therapeutic antibody production
SUBRETINAL INJECTION	Rare diseases	Stargardt disease
		Leber congenital amaurosis 10
	Prevalent diseases	Wet age-related macular degeneration



Source: Company presentation.

A plug-and-play approach to genetic medicines

While Generation Bio has turned to lipid nanoparticles, Code Bio is doing something different.

The group is using a synthetic DNA scaffold, onto which it can attach both a targeting moiety to direct therapy to the correct organ or cells, and a genetic medicine payload. This approach gained validation in February via a **small deal with Takeda**, and Code also has partnerships with two other unnamed pharma companies, its chief executive, Brian McVeigh, says.

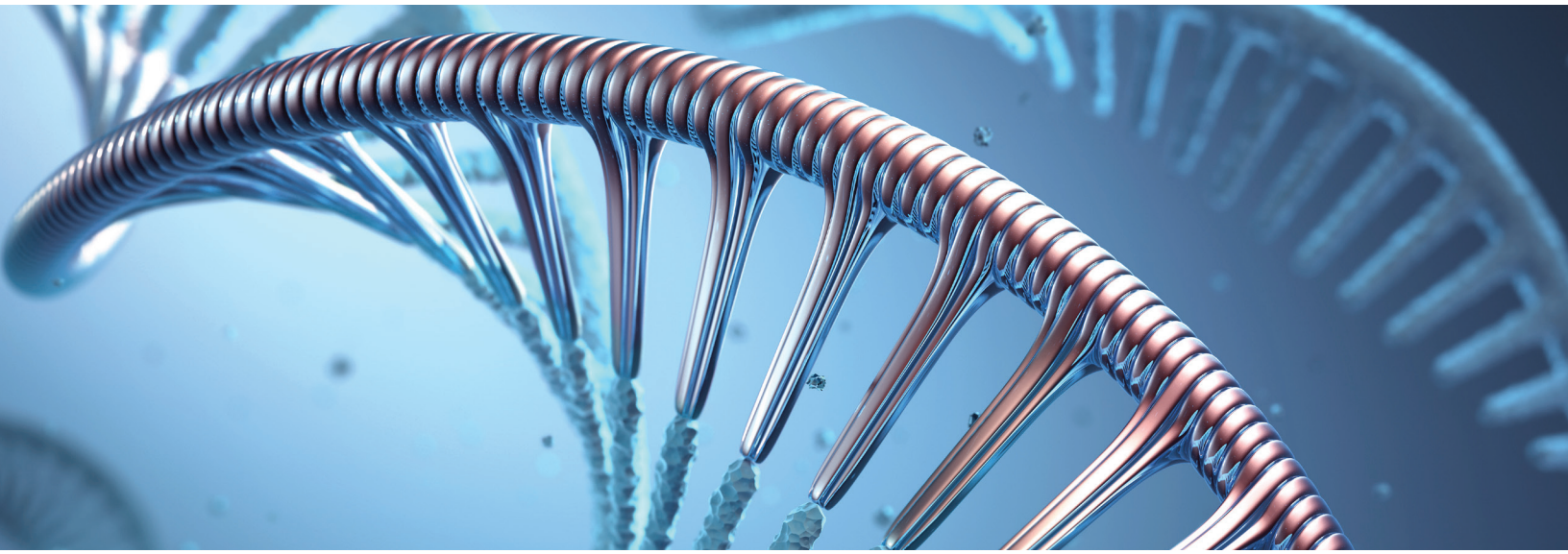
Details on the Takeda agreement are thin on the ground, but the companies will initially develop a liver-directed gene therapy. The Japanese group has options on up to four programmes in total, which could cover liver and brain-directed projects.

Better targeting?

Code's scaffold, known as 3DNA, shares some of the advantages seen with other non-viral delivery approaches using LNPs. These include the ability to deliver large cargos and a lack of immunogenicity, opening the door to redosing.

But Mr McVeigh is keen to set privately held Code apart from the LNP players, saying: "The only similarity between us and LNPs is the adjective 'non-viral'."

He reckons that Code's approach could have a big advantage over LNP-based delivery in its ability to target specific cells or tissues. LNPs are typically drawn to the liver and while companies are working on LNP projects designed to travel to other organs, Mr McVeigh highlights the "high degree of tissue selectivity" that Code can achieve with its targeting molecules.



These molecules can include peptides, antibodies and small molecules. Takeda is interested in brain-directed assets, for example, which will use a targeting moiety that can cross the blood-brain barrier.

As well as potentially being more specific, Code's approach could be simpler from a manufacturing perspective. With LNPs, organ selectivity – so-called "tropism" – is dictated by the make-up of the particle itself, whereas Code can simply "plug" the targeting moiety into its existing scaffold. As Mr McVeigh puts it: "We don't have to engineer a new capsid or new LNPs with specific tropism for certain tissues."

This could speed up the discovery process, he says. "We can make quantities of delivery scaffold and just have it at the ready. And as we think about the diseases we want to work on, it's simply a matter of identifying the best targeting moiety to conjugate as well as the best payload to deliver. We can immediately start working on a formulation."

Avoiding LNPs could also help Code sidestep the intellectual property wrangling that has reached a head recently. This saw **Arbutus and Genevant suing Moderna**, then **Alnylam suing both Moderna and Pfizer**, then Pfizer's partner Acuitas reacting with a lawsuit of its own against Arbutus.

Still, LNPs are becoming something of a known quantity after their use in mRNA Covid vaccines, and Code's scaffold is completely different. The group will need to convince regulators that its approach is safe before it can take it into humans.

"We can make quantities of delivery scaffold and just have it at the ready. And as we think about the diseases we want to work on, it's simply a matter of identifying the best targeting moiety to conjugate as well as the best payload to deliver. We can immediately start working on a formulation."

Brian McVeigh, Code's chief executive

Mr McVeigh is convinced that the scaffold, which has been engineered so as not to cause an immune response, is inert. "With the naked scaffold we've gone out for several months in several different animal models and haven't seen any issues there."

However, he acknowledges: "When we start attaching things, that's when we'll see what happens."

Payloads

For its payloads Code is looking across the spectrum, from gene therapies to RNA interference to gene editing.

Its two lead projects are designed to showcase the advantages of Code's technology: the ability to deliver large genes and to target organs other than the liver.

One is a gene therapy for Duchenne muscular dystrophy, which is caused by mutations in the large dystrophin gene. Conventional AAV-based gene therapy players, such as Sarepta, have tried to get around the size of this gene by using a truncated version of dystrophin, **so far with unconvincing results**.

Code's second project is a pancreas-directed short interfering RNA for type 1 diabetes.

As for gene editing, "we're just beginning to move forward with our activities", the chief exec says, although he will not disclose whether Code will be delivering Crispr/Cas9 editing or something different.

Still, the group's unique selling point is not its genetic medicine technology, but rather its scaffold and linkers, as well as what Mr McVeigh describes as its proprietary targeting library. "We're different – this is a new modality," he concludes.

Code Bio's internal pipeline

INDICATION	DESCRIPTION	PRE-CLINICAL DEVELOPMENT
Duchenne muscular dystrophy	Gene therapy	
Type 1 diabetes	RNAi interference	

Source: Company website

Bringing gene editing to the masses

So far, gene editing has been largely limited to rare diseases, but Verve Therapeutics hopes to change this. The group is focused solely on once-and-done therapies for cardiovascular disease using in vivo base editing.

This might sound like a hard sell, given the inherent risk of gene editing. But Verve reckons it can rival currently marketed anti-PCSK9 approaches by improving compliance and thereby reducing the morbidity and mortality that are associated with very high cholesterol levels.

The preclinical-stage group's share price is well off its peak, but it is still worth around $1bn, so at least some investors are convinced.

Safety first

Verve's chief scientific officer, Andrew Bellinger, says safety was a prime consideration when the group was developing its projects. "We made the decision early on that we were not going to use viral delivery. It doesn't make sense from a safety standpoint or a cost standpoint."

The company is instead using LNPs. Mr Bellinger says that LNPs have been validated by both Covid vaccines and Intellia's amyloidosis gene-editing contender NTLA-2001. But NTLA-2001 uses Crispr/Cas 9 to do its editing, while Verve has plumped for more precise base editing technology, licensed from Beam Therapeutics.

> "We made the decision early on that we were not going to use viral delivery. It doesn't make sense from a safety standpoint or a cost standpoint."
>
> **Andrew Bellinger, Verve's chief scientific officer**

Again, this decision was based around ensuring safety, Mr Bellinger says. "We demonstrated that with base editing we can make single base pair change, highly reproducibly, in exactly one spot in the human genome. This precision is a key part of what's going to make this a therapy that can be safety administered to millions of people."

Crispr/Cas 9, meanwhile, relies on making double-strand DNA breaks, which are then repaired. There are concerns that improper repair could **result in chromosomal abnormalities**, including translocations that could lead to cancer.

PCSK9

Verve is a long way from proving that its approach is safe in humans. The group plans to start treating patients with its lead project, VERVE-101, in the second half of this year; this would make it the first in vivo base-editing asset to enter the clinic, ahead of efforts from Beam.

VERVE-101 might be novel in some ways, but in another it is very familiar: it is designed to turn off the PCSK9 gene in the liver. Anti-PCSK9 MAbs from Sanofi/Regeneron and Amgen have been available to treat stubbornly high LDL cholesterol since 2015, while Novartis's long-acting product Leqvio, a small interfering RNA that inhibits PCSK9 production, got the nod late last year.

Verve believes that with a once-and-done therapy it could disrupt the PCSK9 market.

One problem with the current MAbs, which are subcutaneously injected once or twice a month, is compliance. "The reality is that patients go on therapy for a brief period of time, then they stop taking their medicine or their insurance changes; many different things can happen and their LDL gets out of control again," Mr Bellinger says.

He does not believe that VERVE-101 has been made redundant by the entrance of the Novartis drug. "[With Leqvio] patients have to come into the doctor's office every six months, and that might not always happen all that consistently."

But Stifel's Mr Ha, who covers Verve, says that the Leqvio schedule "jibes really well" with current clinical practice, which involves patients getting a check-up with their cardiologist around every six months.

He is cautious about Verve's prospects, citing commercial and regulatory considerations. On the regulatory side, Mr Ha questions how the FDA might view a genetic medicine going after LDL-C reductions versus diseases like spinal muscular atrophy with no other options.

Even if VERVE-101 reaches the market, he has doubts about the appetite for the therapy among cardiologists and patients. "The fundamental issue here is you're changing your DNA. Can we get comfortable with the unknown risks and administer this drug?"

Mr Bellinger points out that atherosclerotic cardiovascular disease is "the leading cause of death in the world today, despite the fact that we have a lot of therapies". That highlights the need for new options, he says.

And Mr Ha concedes: "It's a huge market, so any kind of penetration is going to be a lot of upside for Verve."

The company will initially test VERVE-101 in heterozygous familial hypercholesterolaemia, which affects around two million patients across the US and Europe. It then hopes to expand into patients with atherosclerotic cardiovascular disease, addressing eight to 10 million people in the US "and a similar number in Europe", Mr Bellinger says.

Verve Therapeutics' pipeline

PROJECT	TARGET	INDICATION	LEAD OPTIMISATION	IND-ENABLING STUDIES
VERVE-101	PCSK9	Heterozygous familial hypercholesterolaemia		
UNNAMED	ANGPTL3	Homozygous familial hypercholesterolaemia		

Source: Company presentation

Gene editing for infectious diseases

While Verve is looking at cardiovascular disease, the private group Excision Biotherapeutics has another unusual target: infectious diseases.

Its lead project, EBT-101, is an in vivo Crispr/Cas9 gene-editing approach that the company hopes will be a cure for HIV. Excision just started its first-in-human trial.

EBT-101 uses in vivo Crispr/Cas9 to make three cuts in the HIV genome, removing large portions of viral DNA from the host genome with the aim of deactivating the virus.

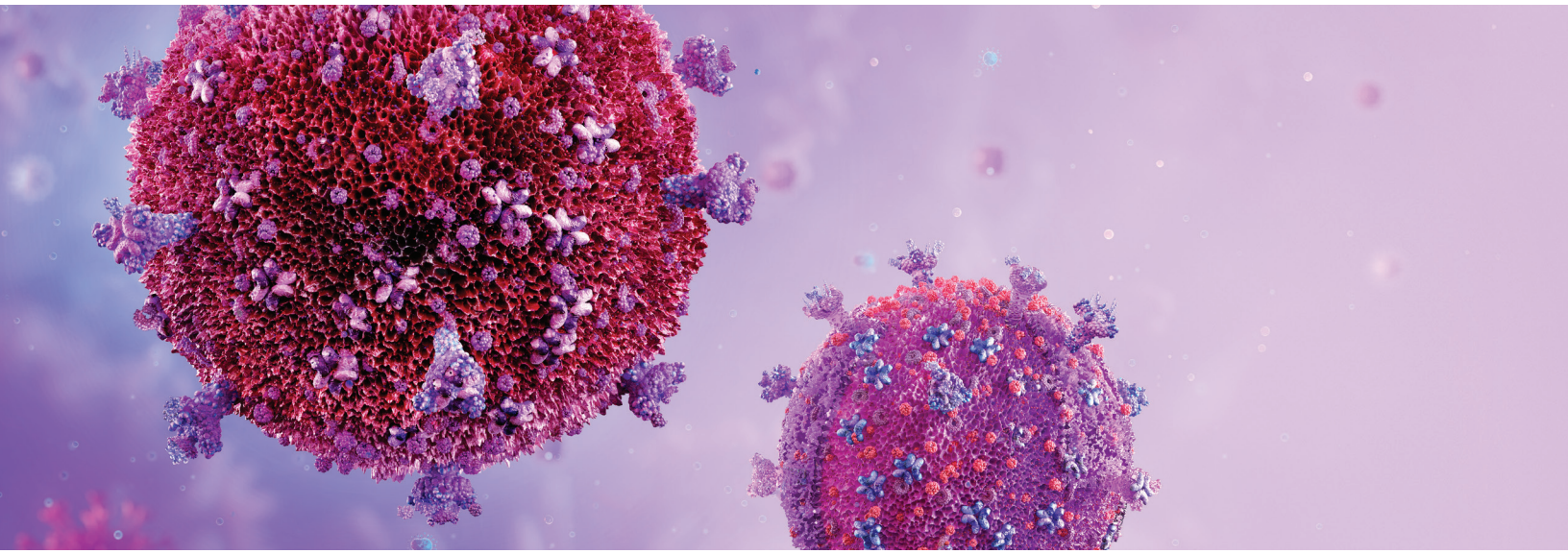
There are many questions still to answer with such a novel approach. As with all Crispr-based projects, there will be concerns about off-target cuts causing unintended consequences, and this could be a particular worry for EBT-101 given that it makes multiple cuts.

But Excision's chief executive, Daniel Dornbusch, does not believe that this will be an issue, in part because the asset is homing in on viral rather than human DNA. The "vastly different" sequences should minimise the chance of EBT-101 also hitting a site in the human genome, he reckons.

Another factor in Excision's favour, he says, is the fact the group is not trying to introduce a new gene into human DNA, something that "can potentially disrupt function".

"All we're trying to do is remove DNA that wasn't supposed to be there in the first place. We're using Crispr in a way that is relatively similar to how it evolved in nature, to defeat viruses. As a result, we have not seen any off-target cuts in any of our preclinical models," he says.

There is also the question of what happens to the excised viral DNA – could it integrate into the host genome and cause problems? "We've used PCR to look for the sequences that we've removed, and we don't see it in cells or animals afterwards," Mr Dornbusch replies. This suggests that the DNA in question has been degraded, he says.



When the breaks are repaired, there is often some viral DNA left behind in the host DNA, the chief exec says, but adds: “These segments are not sufficient to establish an infectious viral particle and are also not coding regions that would create an issue in a host cell.”

Total or partial elimination

Another question is how much of the virus will need to be eliminated to produce a cure – particularly as EBT-101 is designed as a one-time therapy. In HIV, viral reservoirs are found in tissues including the spleen and bone marrow, but Mr Dornbusch reckons that EBT-101 will not need to hit every cell to be effective.

He points to the existence of a rare group of patients known as “post-treatment controllers” who do not have viral rebound after stopping anti-retroviral therapy, despite still having some virus in their blood.

Even if partial elimination is enough in HIV – and that still needs to be proven – it will probably not be the case for all viruses. In hepatitis B for example, where Excision also has plans, “we believe we need to get to just about every sequence”, Mr Dornbusch says. For this, redosing will be required.

EBT-101 is delivered via an adeno-associated viral vector, AAV9, meaning it can only be given once, for reasons outlined above. For a redoseable treatment a different delivery method will be required – Mr Dornbusch says this will “most likely” involve lipid nanoparticles, which are not associated with the same immunogenicity.

Another area where Excision has options is its Crispr enzyme of choice. Mr Dornbusch mentions that Excision has a licence from UC Berkeley covering Cas12, which could be useful given **the recent Crispr/Cas9 patent ruling in favour of the Broad Institute**.

Even if Excision’s technology evolves, the **phase 1 trial of EBT-101** will be an important test of the potential of this approach. Initial data, on safety at least, should be available by the end of the year.

And the group does not look like it will have any trouble recruiting for the nine-patient US study, even though the vast majority of HIV patients in that country have well-controlled disease. “Many more people have enquired about getting on this study than we can accommodate,” the chief exec says.

Excision Biotherapeutics’ pipeline

PROJECT	INDICATION	DESCRIPTION	DISCOVERY	PRE-CLINICAL	PHASE 1
EBT-101	HIV	AAV9-delivered Crispr/Cas9			
EBT-103	Progressive multifocal leukoencephalopathy/ JC virus	AAV9-delivered Crispr/Cas10			
EBT-104	Herpes simplex virus	AAV-delivered Crispr/CasX			
EBT-107	Hepatitis B	Non-viral-delivered Crispr/CasX			

Source: Company website.

Gene coding: the final frontier

While the previous companies in this report are involved in either gene therapy or gene editing, Saliogen believes its approach is different again. The private developer has even coined a new term to describe it: "gene coding".

And its chief executive, Ray Tabibiazar, makes a bold claim: "Our platform allows you to put any size [of] DNA into the genome."

He is nothing if not ambitious, saying: "Our vision is that genetic medicine will become as common as any other therapeutics like small molecules or antibodies." The company has a very long way to go to make this a reality: its pipeline is still preclinical, and Mr Tabibiazar will not say when Saliogen hopes to take its first asset into human trials.

Gene coding vs gene therapy

On paper, the gene coding approach sounds almost too good to be true. Theoretically, inserting a gene into a patient's DNA and making a permanent change to their genome could get around the lack of durability that has been seen with conventional gene therapies.

And while current gene editing approaches can make changes to a patient's genome, at present these changes are relatively small. Base editing, being developed by the likes of Beam Therapeutics and Verve Therapeutics, only targets single mutations; Crispr/Cas9 can insert longer stretches of DNA, but there is still a size limit.

Without this limit, Saliogen reckons it will be able to target diseases in which large genes are affected. Both rare conditions, like the genetic eye disorder Stargardt disease, and more common ones, such as familial hypercholesterolaemia, are in its sights.

Like many of the next-generation gene therapy and editing approaches, Saliogen's therapies are being delivered via lipid nanoparticle, allowing the delivery of large genes, a lack of immunogenicity and easier manufacturing.

> "Our vision is that genetic medicine will become as common as any other therapeutics like small molecules or antibodies."
>
> **Ray Tabibiazar, Saliogen's chief executive**

Mammalian vs bacterial

Saliogen is using the LNPs to deliver the donor DNA required and mRNA that encodes for Saliogase, a mammalian enzyme. This makes Saliogen's approach different from Crispr/Cas9 gene editing, which employs a bacterial enzyme.

The group says that Saliogase "seamlessly" inserts the desired DNA into precise locations in the host's genome, without the double-strand breaks that are seen with Crispr/Cas9. These double-strand breaks have raised concerns about chromosomal abnormalities such as translocations.

As Mr Tabibiazar puts it: "The mammalian enzyme has co-evolved with the mammalian system throughout evolution, so there's a better fit, almost like software and hardware."

However, as with any brand-new technology, Saliogen will have to prove that its system is safe. One way the group hopes to mitigate risk is having Saliogase expressed only transiently. "And during that transient time period it grabs the donor DNA and inserts it into the host DNA."

Saliogase might not hang around for long, but the changes it makes will be permanent. Mr Tabibiazar is well aware that the group needs to ensure that the donor DNA "doesn't go somewhere you don't want it to go or interact with other genes that you don't want it to interact with".

Saliogen's solution is "insulators" that are designed to "flank the gene of interest to protect against any unintended activity of nearby promoters or enhancers in the genome after the gene of interest is inserted".

The group is also using DNA markers to ascertain where the new genetic code has integrated into the genome. Regulators will surely be keeping a close eye on these potential issues before allowing the company's technology to be tested in humans.

> "We need good science and good people, and we also need a little bit of luck. But I can only control the first two."
>
> **Ray Tabibiazar, Saliogen's chief executive**

As for intellectual property, which **has caused issues in the Crispr world**, Mr Tabibiazar says: "We're building a very robust IP portfolio," adding that the group has discovered several more mammalian enzymes.

Saliogen came out of stealth mode in March 2021 with a $20m financing, and raised another $115m in January. There is clearly still interest in next-generation genetic projects, despite the string of recent setbacks in the wider gene therapy space.

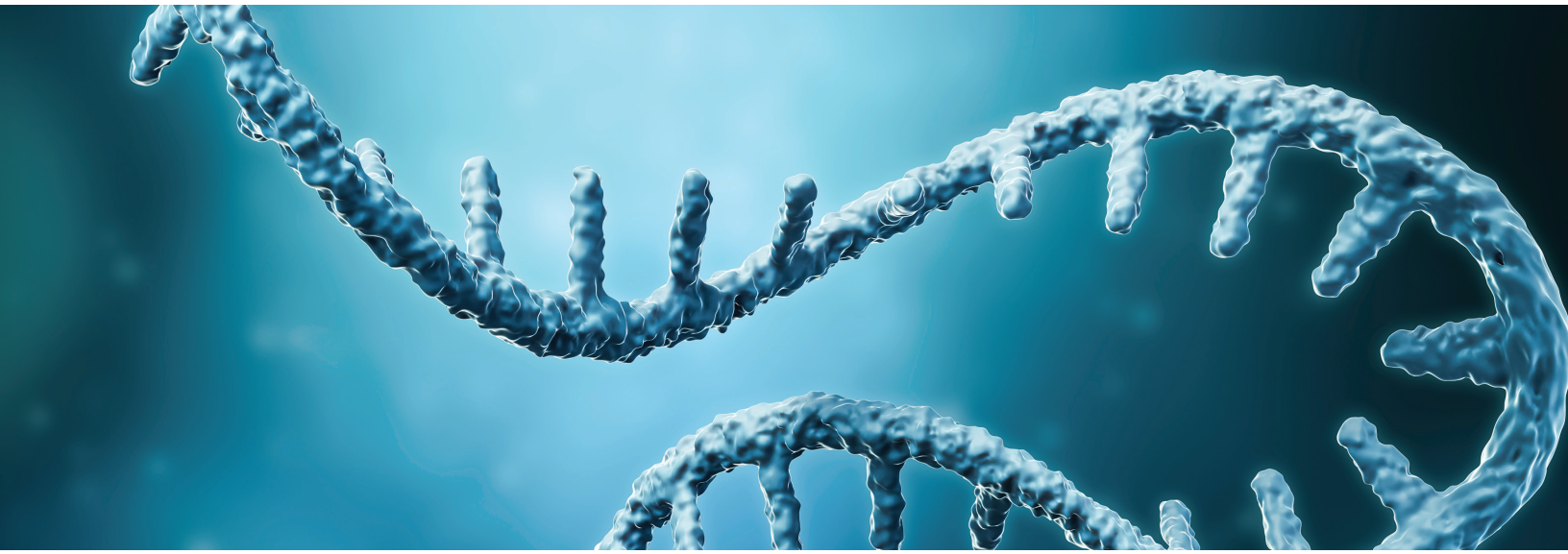
"Our investors realise the potential impact of our technology is massive," the chief exec says. "But they also realise that transforming science requires a lot of hard work, and that's the nature of being early."

He concludes: "We need good science and good people, and we also need a little bit of luck. But I can only control the first two."

Saliogen's pipeline

TISSUE	INDICATION	DISCOVERY	LEAD OPTIMISATION
LIVER	Hypertriglyceridaemia	■	■
	Lipoprotein (a)	■	■
	Familial hypercholesterolaemia	■	■
RETINA	Stargardt disease	■	■
	Usher syndrome	■	
	Retinitis pigmentosa 1	■	
	Retinitis pigmentosa 25	■	
HEART	Congestive heart failure	■	
	Catecholaminergic polymorphic ventricular tachycardia	■	
	Hypertrophic cardiomyopathy	■	
LUNG	Cystic fibrosis	■	
BONE MARROW	Undisclosed	■	
KIDNEY	Undisclosed	■	

Source: Company website.



Pricing considerations

The approaches outlined above are clearly very early and still have much to prove. If they do progress, the question of price will become ever more pressing, as these projects will need to be affordable if they are to help move genetic medicines into the mainstream.

For now, the executives running these developers are understandably reluctant to talk specifics on pricing. But they are all keen to highlight the potential manufacturing and cost advantages of their projects over conventional gene therapies, which have so far been notoriously expensive. Broadly speaking, LNPs can be more easily produced at scale than AAVs, and thus should allow a lower price point for assets using the former delivery method.

Code Bio's Mr McVeigh also highlights the relative simplicity of its scaffold-based approach. "If you think about a situation where we're using a peptide as a targeting moiety, and we're delivering a gene construct or an siRNA, these are all synthetically made components. And they're readily available."

However, he adds that the price of that group's projects will vary, depending on both the targeting moiety and the payload.

A redoseable genetic medicine could also shift the risk away from payers, although current gene therapies have often involved risk-sharing arrangements.

Pricing issues will be particularly pertinent for Verve and Excision, given that these groups are targeting common diseases.

All Verve's Mr Bellinger will say, for now, is that VERVE-101 "is not going to be priced at $2m". Stifel estimates that its price will be around $200,000 in the US – this compares with around $6,000 per year for current PCSK9 therapies, **including Leqvio**. Still, the PCSK9 MAb makers had **once hoped to command a higher price for their products**, and sales have fallen short of expectations.

Excision, meanwhile, has an ethical consideration with EBT-101: developing nations have borne the brunt of HIV but are least able to afford genetic medicines.

Mr Dornbusch acknowledges this, saying: "How do we make sure we can engineer and commercialise a product that can be used around the world? That has to be paramount to every programme in our pipeline."

He believes that the sheer scale of HIV and other infectious diseases should help here. "With scale, we believe we can reduce cost of goods quite dramatically."

He likened the current gene therapy market to the initial computer industry, when devices were the size of rooms and accessible to only a few people. "It required many innovations to put cell phones in everyone's pockets. It hopefully won't take quite as many for gene therapy, but I believe it's a similar trajectory."

It is far from clear whether genetic medicine will ever reach this point. The next few years will be a big test of this burgeoning field.

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