Gene therapy players sensing light at the end of the tunnel

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Although there might be light at the end of the gene therapy tunnel as Amsterdam Molecular Therapeutics’ (AMT) Glybera awaits the judgement of European regulators, there remains little doubt that gene therapy remains one of the riskiest areas of drug discovery.

However whilst companies working in the field agree that life remains tough, they are also reporting a thawing of opinions from many quarters. Importantly, European regulators are establishing protocols and remain highly co-operative, and big pharma is showing flickers of interest. Investors, perhaps understandably, remain highly sceptical. The landscape is certainly changing, whilst it awaits the validation that the Western world’s first approval would bring.

Several risks

There are several risks inherent with gene therapy - scientific, regulatory and, yet to be tested, the challenges that figuring out reimbursement will bring. Numerous complications have been seen and are likely to arise at each step of development, and the regulatory landscape in particular is rocky, as the regulators themselves get to grips with such novel therapies and processes.

Currently, most development is targeted at a single gene and the majority of investigation is in the areas of cancer and orphan indications. AMT says that 80% of orphan indications are thought to be the result of a single faulty gene.

The scientific obstacles that genomic product development has thrown up include immune responses to the material or vector, which at best renders the therapy ineffective and at worse causes huge and deadly side effects. There is also the potential for ‘insertional mutagenesis’, where inaccurate insertion of the new gene can trigger tumour growth.

Furthermore, the host cell must have substantial survival ability to reproduce many times over, in order to generate sustainable efficacy. If patients need repeat treatments, an immune response can be exacerbated.

Two cases where gene therapy went horribly wrong are often cited as reasons why many researchers and investors backed away from this space.

In 1999, Jesse Gelsinger, a sufferer of ornithine trscarbamylase deficiency (OTCD), entered a gene therapy trial which involved injecting an adenovirus carrying the protective gene into one of the main arteries in the liver. Shortly after receiving the dose his ammonia levels rose to dangerous levels, he suffered brain damage and organ failure and fell into a coma, eventually dying.

Then in 2002, France and the US suspended gene therapy research after children developed a leukaemia like illness in a trial aimed at treating severe combined immune deficiency.

Looking forward

Despite a long history of setbacks, many believe that interested parties are increasingly looking to the future rather than the past.

“A lot of people who had an ingrained perception that gene therapy is too risky and will never work, are rapidly changing their minds,” AMT’s chief executive Jörn Aldag tells EP Vantage. He says that the big pharma companies are increasingly willing to at least look at gene therapy projects, even if they are not actually signing formal deals (EP Vantage Interview - AMT hoping to pop the cork with Glybera approval, August 25, 2010).

“We ended up having two or three discussions with one big pharma company (about a haemophilia project) who initially said they were not looking at gene therapy,” he says, adding that in the end, they walked away.
“The statement ‘we are not interested in gene therapy’ has changed,” he says.

**Deals being signed**

A couple of notable deals with big pharma companies have been signed in the last couple of last years.

In April 2009, Sanofi-Aventis entered into a research collaboration with Oxford BioMedica to develop gene-based medicines for ocular diseases, using the company’s LentiVector gene delivery technology. The company has already generated a Parkinson’s disease product, ProSavin, from the platform, which is in phase II studies.

“Before this, you would be quite surprised that Sanofi were going into gene therapies prior to clinical implementation, so there must have been a de-risking element. For us, we had accumulated two years’ data in man on our platform,” John Dawson, chief executive of Oxford BioMedica, tells EP Vantage.

And in January this year, Novartis signed a deal with gene therapy player GenVec, for worldwide rights to TherAtoh, an Atoh1 gene therapy for ear disorders still in pre-clinical development.

**Not convinced**

Still, not all are convinced that this means big pharma is about to launch a big move into the gene therapy space.

“We are still a long way from getting the main pharma guys to buy in, in a big way, they are really just touching it on the sides,” says Samir Devani, biotechnology analyst for NomuraCode.

Mr Dawson concurs, adding that ocular therapies could present less of a challenge than areas that would need systemic delivery.

“[Sanofi-Aventis] liked ocular,” he says. “It was like dipping a toe into the waters of gene therapy, as you don’t need to make much of the stuff, and you know where you’re sticking it, so it’s less risky.”

He points out the deal was signed in the wake of “an accumulating tide of data” in the gene therapy space, including strong results from studies of Targeted Genetics’ AAV-RPE65; the adeno-associated vector-based candidate was shown to significantly improve sight in retinal dystrophy patients.

Still, Sanofi also has a phase III gene therapy, Temusi, that is due to report results later this year, one of the few products that is attracting sales forecasts from equity analysts (Therapeutic focus - Will hopes evaporate as gene therapy pipeline flows?, August 25, 2010).

**Regulators**

Few companies have got far enough to start having approval discussions with regulators, a process complicated by the fact that regulators themselves are getting to grips with the issues of this novel technology. In Europe, this is overseen by the European Medicine Agency's Committee for Advanced Therapies (CAT).

“The CAT, the body set up to support the development of rare diseases and novel approaches, is looking at something without a benchmark. If you develop a new statin the benchmark is known. In gene therapy the benchmark doesn’t exist. There hasn’t been an adeno-associated virus [vector-based therapy] in registration, and therefore lots of questions they are asking are because they are trying to establish a benchmark,” AMT’s Mr Aldag says.

“You can compare [the situation] to cancer vaccines,” Oxford BioMedica’s Mr Dawson says. “Dendreon went through this recently with Provenge – that was a sign that the FDA was willing to accept that it can attack tumours. Gene therapy is getting to the point where we are demonstrating that it is working. There is a pathway to be set; the pathway for cancer vaccines was set by Dendreon.”

**Co-operation**

Companies report that regulators do genuinely want to bring these therapies to market. They take a collaborative stance in trial design, and work hand-in-hand in the nascent stages of technology development to design an effective platform.

“It has been very much co-operative,” say Mr Dawson, with respect to the ProSavin clinical process.

Mr Aldag echoes the sentiment, saying: “The discussions we are having with [the CAT] are extremely constructive. The CAT is supporting us and has an interest in getting things approved.”

Many point to Ark Therapeutics as example of failure in this space, but this product failed because of questions
over efficacy, rather than the regulator having a problem with gene therapy itself.

“What the [Ark] regulatory process resulted in was practically validation of gene therapy, even though this specific product didn’t make it. There is no evidence that [the regulators] were criticising the gene therapy approach or thought there was too much risk coming from that.” AMT’s Mr Aldag says.

**Investors**

Of course, even if the regulatory environment appears to be improving, in Europe at least, and big pharma is beginning to show a bit more interest, money still has to be found to fund this research. After years of getting burnt investors are understandably reluctant to stump up the cash.

"Investors are not only taking product development risk and regulatory risk, the regulatory risk is also uncharted territory. There’s enough risk in [biotechnology] this sector already without having to take on all that,” NomuraCode’s Mr Devani says.

"It’s going to be a long time until someone makes money out of gene therapy. There’s so much more risk than with average biotech,” he adds.

Still, he concurs that approval of Glybera, if it happens, will be a pivotal moment.

"It will probably be a loss leader but it will make the lives of the other coming behind it a lot easier."

As such, there are signs that confidence in gene therapy is building. Pathways to approval are being forged and the developers that have so far been brave enough to take the plunge have, at the very least, helped with their establishment. Fundamentally though, there is still belief in the concept from all sides. If one candidate can get its foot in the door, perhaps the industry can look forward to that new era it has long been hoping for.