Arrival of a ground-breaking gene therapy

The precedents set by Zolgensma

The US Food and Drug Administration's approval of the gene therapy Zolgensma on 24 May marked an important juncture in biotech history. The therapy is intended as a single life-time administration for spinal muscular atrophy, a regulatory milestone. Shortly thereafter the sponsor, Novartis, announced a price of just over $2 million for the product, a record for the industry.

The two decisions have fundamentally altered the trajectory of innovative medicines, not only in terms of what the new gene therapies can achieve for patients, but what society may be willing, or able to pay for them. This article is a case study of Zolgensma, highlighting some of the crucial decisions leading up to its registration and commercialisation.

Zolgensma (onasemnogene abeparvovec-xioi) is an adeno-associated virus (AAV) vector-based gene therapy that targets the survival motor neuron 1 (SMN1) gene, the cause of spinal muscular atrophy. The vector delivers a fully functional copy of the SMN gene into motor neuron cells which control muscle movement throughout the body. According to the FDA, a one-time treatment results in the expression of the SMN protein in a child's motor neurons, which improves muscle movement and function and in the survival of the child.

The current drug was developed by AveXis Inc, now owned by Novartis, on the basis of research conducted by Brian Kaspar, the company's scientific founder and currently, its chief scientific officer. Dr Kaspar and colleagues were authors of a paper in *Nature Biotechnology* in 2010 describing the successful use of a self-complementary adeno-associated virus 9 to deliver the SMN gene into mice with spinal muscular atrophy.[1] That same year, AveXis was founded with a licence to technology developed by the Nationwide Children's Hospital of Columbus Ohio, US where Dr Kaspar led a translational laboratory in neuroscience.

The French connection

None of these medical developments would have been possible without the help of some fundamental genetic research. Fifteen years before the publication of the *Nature Biotechnology* paper, a science team at the French National Institute of Health and Medical Research pinpointed the genetic cause of spinal muscular atrophy. At the time, researchers had hypothesised, on the basis of natural history studies, that the gene responsible for spinal muscular atrophy was located on the long arm of chromosome 5. This was in 1992. Three years later, Judith Melki and colleagues at the institute were able to identify the rogue gene using a technique known as positional cloning. They mapped the mutated gene to chromosome 5q13 and identified two nearly identical copies: survival motor neuron 1 (SMN1) and SMN2. Their findings were published in *Cell* on 13 January 1995.[2, 3]

The survival motor neuron 1 (SMN) gene creates the SMN protein which is essential for motor neuron development. SMN2 also produces the protein, but only a small amount is functional.[4] In any case, normal gene and normal protein production are critical to human development.

"All cells need SMN including muscles and the liver because SMN uses a very basic biological mechanism, the maturation of RNA, leading eventually to the synthesis of all proteins in cells," said Serge Braun, scientific director of AFM-Téléthon, in an interview with *MedNous*. AFM-Téléthon is the French Muscular Dystrophy Association and finances the research laboratory Généthon which is in the same location.

In mutated form, the SMN gene directly affects development, starting in infancy. The incidence of spinal muscular atrophy in the US is said to be one out of every 10,000 live births. Scientists have identified four types of the disease, of which Type 1 represents about 60% of all cases. Type 1 strikes in early infancy and results in death before two years of age. Type 2 appears between the ages of six and 18 months with death after two years. Types 3 and 4 are less severe but nonetheless disabling.

An important figure in translating this basic research into a potential product for patients is Martine Barkats. A former senior scientist at Sanofi SA, she joined Généthon in 2004 to lead a scientific team that was investigating new methods for gene transfer to the central nervous system, in particular to motor neurons using lentiviral and adeno-associated virus vectors.

An important event was the discovery of a vector that could cross the blood-brain barrier. The blood-brain barrier is a layer of cells that line the blood vessels of the brain, forming a tight barrier that prevents toxins and microbes from entering the organ. Medicines that are intended to treat neurological disorders need to cross this barrier – safely – in order to have an effect.

Dr Barkats and her team discovered and tested a serotype of the AAV vector – self complementary AAV9.

The surprising discovery was that the vector and gene could be delivered to motor neuron cells by peripheral administration, which is to say intravenously. In 2007, Dr Barkats filed a patent for the invention with the European Patent Office.[5] The patent relates to compositions and methods for the delivery of therapeutic proteins to the central nervous system using recombinant adeno-virus vectors. Specifically, it describes methods for delivering proteins into the cerebrospinal fluid through peripheral administration.

Two years later, in 2009, she wrote up her discovery in a paper for *Molecular Therapy*.

A crucial decision

By 2010 it had become clear that the work in Paris, France and Columbus, Ohio were running in parallel tracks with researchers in both countries pursuing AAV9-based gene therapies. Both Brian Kaspar and Martine Barkats had made important discoveries which were published in prestigious academic journals. Importantly, Dr Barkats also

had a patent. Then the waters parted.

The management at Généthon decided not to take its invention into clinical development. According to Dr Braun, there were at least two reasons for this: the cost of clinical development was considered too high. Additionally, the injection of a new gene therapy into infants was considered too risky.

By contrast, the risk-benefit calculation at AveXis was different. The AveXis team, led by Jerry Mendell of Nationwide Children's Hospital, decided to proceed with a Phase 1 trial of AVXS-101, as the investigational therapy was called, in 15 infants with Type 1 spinal muscular atrophy. They also decided to start a long-term extension study. In an interview with *SMA News Today*, and published on 28 May, Dr Mendell said the investigators took the controversial decision to give a high dose to infants in the pivotal study.[6]

"This is the highest dose of virus that had ever been given in a clinical trial, and most investigators – and even the FDA – were very concerned about giving this much," he said in the interview. The dose was $1.1x10^{14}$ vector genome per kilogram of body weight. However expert opinion swung around after patients showed a response to the treatment.

The commercial landscape

AveXis started the Phase 1 trial of AVXS-101 in 2014, four years after the launch of the company. When the company started out, there was no approved treatment for spinal muscular atrophy. This soon changed. Ionis Pharmaceuticals Inc, a developer of RNA-targeted drugs, had a partnership with Biogen Inc, and together they developed an antisense oligonucleotide, nusinersen, for the disease. Like the AveXis and Généthon inventions, nusinersen was directed at mutations in chromosome 5q. However, it was designed to bind to and alter the SMN2 gene rather than targeting SMN1. Furthermore, the drug was not intended as a one-time cure; it had to be administered over a lifetime. The clinical data was positive showing a sustained improvement in the motor functions of patients compared with untreated patients. Nusinersen, known commercially as Spinraza, was approved by the FDA in December 2016.

Earlier that same year, AveXis decided to make an initial public offering (IPO) of its shares on Nasdaq. Its Phase 1 study of AVXS-101 was underway and the company had already treated 15 patients. In its IPO prospectus, AveXis said that patients in the study had a favourable safety profile and investigators had observed "compelling preliminary evidence of efficacy, including improved motor function."[7] The company, which had 18 employees at the time, raised $95 million in February, 2016.

Meanwhile in Switzerland, Novartis was starting to expand its gene therapy investments following US approval in 2017 of its chimeric antigen receptor (CAR) T cell therapy Kymriah for cancer. Vasant Narasimhan became chief executive on 1 February 2018 and within two months of his installation the new management team made a bid to buy AveXis. Novartis offered to pay $218 per share for the company, or nearly 11 times the $20 per share price that AveXis had set for its IPO. This made a total consideration of $8.7 billion. As part of due diligence for the acquisition, AveXis negotiated a licence with Généthon for rights to its vector technology, as spelled out in Martine Barkats' patent. The agreement involved an upfront payment to Généthon of €15 million and a royalty rate on future sales of about 5%, according to Dr Braun.

The pricing issue

On 24 May Novartis announced that it will price Zolgensma at $425,000 per annum over five years for a total of $2.1 million per patient for a once in a lifetime treatment. The price was set to compete with Spinraza which is currently $750,000 for the first year of treatment and $375,000 annually thereafter. The independent Institute for Clinical and Economic Review said that given Zolgensma's efficacy the price fell within the "upper bound" of its value-based price benchmark range.

But this may not be the end of the story. The UK's National Institute for Health and Care Excellence is currently evaluating Zolgensma for cost-effectiveness in anticipation of a European regulatory approval. NICE previously refused to recommend Spinraza for reimbursement. But on 15 May, it changed its mind after negotiations with Biogen resulted in an agreement to fund treatment for a limited period, after which the decision will be reviewed. More broadly, the Zolgensma development and approval have set precedents for the industry which will be difficult to change. Zolgensma showed that a high dose of a gene therapy can be safely administered to children. Will this be true of other therapies with other vector types? This may send the regulators back to the drawing board for new guidelines. Finally, does the Zolgensma price represent a new threshold for gene therapy, or will the tolerance for high prices amongst payers break? "If all the other drugs will be as expensive [as Zolgensma] nobody will be able to afford them," said Dr Braun.

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