

Feature

Viral Gene Delivery – Gene Therapy and Beyond

Overview

Viral vectors were originally developed as an alternative to transfection of naked DNA, through their ability to carry, deliver and express foreign genes (and other DNA/RNA products) of interest. A range of viral vectors for use in vaccines and gene therapy (in its broadest sense) are now in the clinic, led by adenoviral and lentiviral vectors. A recent report from Frost and Sullivan has forecast revenues for gene therapy alone to rise from US\$125 M in 2006 to US\$6.5 B by 2011, highlighting the important role that the technology underpins. Current fears generated from an influenza pandemic, the approval of the first gene therapy product in 2004, and the expanded use of viral vectors in drug discovery, are now anticipated to be some of the key drivers to bring this technology to market.

Gene Therapy

Throughout the 1990s, the application of viral vector technology, particularly in the field of gene therapy, was a catalyst for investment in the sector. However, a number of clinical events, most notably the death of a patient at the University of Pennsylvania in 1999 (following gene therapy for ornithine transcarboxylase deficiency), and the halt by the US FDA in 2003 of almost 30 trials using retroviral vectors in blood stem cells (which followed the development of a leukaemia-like condition in two children apparently successfully treated (in France) for X-linked severe combined immunodeficiency (bubble baby syndrome)), suggested that this technology would never satisfy the growing clinical scrutiny. Various complications with toxicology, compounded by poor therapeutic efficacy, have led to the suspension of a number of gene therapy trials worldwide, and from over a 1000 clinical trials currently underway, only one product has so far made it to the market: Gendicine (adenoviral p53) from the Chinese company **SiBiono GeneTech**, which was approved by the State Food and Drug Administration of China (SFDA) in 2003 for head and neck cancer.

Over 60% of gene therapy trials in 2005–06 were for anticancer products, and success from the likes of **Merck & Co.** in developing anticancer vaccines (e.g. its quadrivalent recombinant HPV vaccine Gardasil®) has heightened interest in the development of viral vaccines and gene therapy products for the oncology sector. **Introgen** is one example of a company with a promising portfolio of anticancer gene therapy products. It has five clinical-stage candidates under development, including two in late-stage development: INGN 241 and Advexin®.¹ Advexin is a broad anticancer therapy targeting the p53 gene, and has recently been filed with EMEA under the 'exceptional circumstance' provision for the treatment of Li-Fraumeni syndrome (LFS); the product is also in Phase III trials for head and neck cancer. Like SiBiono's Gendicine, Advexin uses an adenoviral vector to deliver the p53 tumour suppressor gene, and can be used in combination with radiotherapy for the treatment of head and neck squamous cell carcinoma. However, a controversial difference between the two drugs is the scrutiny to which each has been subjected by relevant regulatory authorities: the FDA and SFDA. Clearly, the SFDA has

not been affected by the possible negative impact of failure. Introgen's second late-stage product, INGN 241, is a modified adenoviral vector that carries the melanoma differentiation-associated gene (mda-7); this, also, is in Phase III development for head and neck cancer and, in addition, is in earlier clinical development for a range of other solid tumour types.

Adenoviral vectors are not the only platform being used to develop gene therapy products, and there have been a number of deals among companies wanting to gain access to novel technologies for gene therapy. This is exemplified by two deals made by **VIRxSYS**. The first, in 2003, was with **Takara Bio** to use its Retronectin™-mediated gene transduction technology (Deal no. 13095), and this was followed, in 2006, by a second deal, this time with **Oxford BioMedica**, for its VSV-G viral envelope technology (Deal no. 23670). Both deals concern VIRxSYS' Phase II VRX496 lentiviral vector platform, which is equipped with an anti-sense payload that is transduced into the patient's CD4 T-cells.

Oxford BioMedica itself has broadened and expanded its scope in the gene therapy sector by diverging its gene delivery technology: alongside its proprietary Lentivector™ technology, further technologies include pox viral vectors for use in cancer vaccines, as well as adenoviruses that exploit cell engineering. By this means, the company is likely to be both advancing its suite of products and appeasing investor confidence, following the earlier failures in the gene therapy field.

An analysis of deals in the gene therapy market that are specific to anticancer and antiviral technology provides a good summary of the sector (*Figure 1*). Oncology shows a overall decrease in deal numbers from a high of 31 in 1998 to a low of eight in 2006 – probably a result of the issues surrounding the clinical failures reported in 1999 and 2003. The antiviral sector remained relatively unchanged from 1997 to 2002, followed by a marked increase in activity, which has offset the deal decline in the oncology sector. The majority of the antiviral deals (16 of the 53) involved HIV, and of these, ten were since 2003.

Viral Vectors – Expanding Roles into Vaccine Technology

The flu pandemic, bioterrorism agents and advancing viral vector technology for cancer vaccines have created an upsurge in the vaccine sector that has traditionally been associated with big pharma. Vaccine technology has been developed on numerous

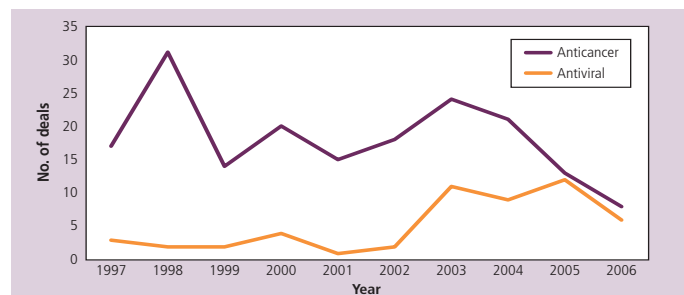


Figure 1 – Deals in the gene therapy market specific to anticancer and antiviral technology in the period 1997–2006 (Source: PharmaDeals® Agreements).

¹ See Deal Tracker, page 15.

	Retroviruses	Adenoviruses	Adeno-associated viruses
Target cell types	Dividing cells	Slow- or non-dividing cells	Slow- or non-dividing cells
Gene expression	Long term	Short term	Short term
Safety issues	Production of replication-competent viruses	Inflammatory responses, cardiotoxicity or brain damage	Risk of mutagenesis and production of replication-competent viruses

Table 1 – Key Properties of Viral Vectors

(Source: Gene Delivery Group at the University of Birmingham).

platforms, all with associated problems. For example, DNA vaccines are proving weak at eliciting antibody responses, and protein vaccines are similarly poor at developing T-cell responses. Hence, the hope is that viral vectors will bridge the efficacy gap. Viral vectors offer a number of advantages, including the ability to engineer vaccines for defined targets, a choice of vectors with different and distinct benefits (Table 1), and the ability to produce large amounts of vaccine cost effectively in cell culture.

Large companies associated with vaccine development include **sanofi pasteur** and Merck, alongside a host of smaller companies, including **Lentigen**, which is validating the use of lentiviral vectors to deliver genes of an avian or seasonal flu virus. The company is targeting seasonal and pandemic influenza through its lead HIV-based lentiviral vector technology, LentiMax™, which can produce vaccines containing haemagglutinin neuraminidase in as little as 5 weeks.

One company that has expanded its adenoviral vector technology into a range of areas is **GenVec**. Its HIV vaccine, both alone and in combination with a plasmid DNA vaccine prime, is currently in Phase III trials. The study is in collaboration with the NIH's **Vaccine Research Center**, and GenVec has recently signed a deal with the NIH's **National Institute of Allergy and Infectious Diseases** (NIAID) to receive up to US\$52 M under a possible 5-year contract (Deal no. 25483). This follows earlier adenovector-based vaccine-funding agreements with both the NIH and the **US Naval Medical Research Centre**.

Bioterrorism has been a major catalyst for investment into vaccine technology. Since 2004, half of the 11 deals that concern viral gene delivery have been associated with bioterror. These are typified by **Cyto Pulse Sciences** working with the **US Army Medical Research Institute of Infectious Disease** on a Marburg DNA vaccine (Deal no. 21579); the Marburg virus is on the US Category A list for biodefence threats. With the US ever expanding on the 'war on terror,' combined with a possible flu pandemic (which threat has itself led to hugely increased investment by the US Government in vaccine development and stockpiling),² this trend will continue, and offers an opportunity for companies wishing to expand their vector technology into further fields.

Drug Discovery

Viral vectors have potential as drug discovery tools in areas such as target validation, transgenic animals and generation of engineered cell lines. By using recombinant viral vectors to deliver genes to the cell, researchers can gain insight into specific genetic mechanisms.

The development of cell-based assays has traditionally involved stable cell lines to produce the targeted proteins, but the specific expression of genes of interest at predefined levels is difficult to achieve. A novel approach to alter gene expression is being

developed through a collaboration between Lentigen (using its LentiMax technology) and **Dharmacon** to develop and manufacture lentiviral expression reagents for the delivery of short hairpin RNA (shRNA) expression vectors into cells, using RNAi-mediated gene silencing (Deal no. 25146). shRNA is useful where long-term gene suppression is required, or where the cells are resistant to other delivery methods. **GE Healthcare** has launched a range of adenoviral vector gene delivery systems through its AD-A-Gen technology, in which the vectors are fused to an epidermal growth factor or a response element controlling the expression of a nitroreductase reporter gene. This technology can be applied to cell-based assays for drug target validation and lead compound profiling. While increased scrutiny and poor efficacy affects the therapeutic roles of viral vectors, drug discovery offers another route to adapt the technology to a rapidly developing sector.

Viral vectors for siRNA are also being developed for therapeutic purposes. Lentiviruses, retroviruses and adenoviruses are all utilised for siRNA, and the first siRNA based therapy, which is being developed by **Acuity Pharmaceuticals**, entered Phase II trials in 2005 for the treatment of wet age-related macular degeneration.

How has the Sector Changed?

A number of drivers have made the sector more optimistic. These include the existence of approved and late-stage products, the success of cancer vaccines, the development of novel platform technologies, and improvements in manufacturing. In the mid-1990s, the advancing use of viral gene delivery was an area typified by industry and academia working as a one to advance a novel, yet untested, therapeutic area. Gene therapy was traditionally associated with cures for monogenic diseases such as Huntington's disease and cystic fibrosis, but these have low patient populations, hence are unlikely to provide blockbuster returns. However, the arrival of Gendicine, and a pipeline of Phase III/ preregistration products, has indicated that gene therapy is a reality rather than a possibility.

These developments have resulted in a change in disease focus, and also a change in the focus of pharmaceutical companies and the associated investment community from a 'proof-of-principle' to a 'competitive' outlook – with an expectation that products can and will enter the market. This is in marked contrast to an industry in which post-1999 investor enthusiasm had been dampened by the initial failure and considerable scrutiny to which viral vector technology had been subjected. Evidence for growth in this technology can be seen from both the rise in the number of virus-based gene therapy companies – from 44 in 1995 to over 190 at present – and from some major financing agreements since 2005: **VIRxSYS** raised US\$50 M in 2005, and US\$20 M in 2006 (through Series F and G fundings); **Celladon**, which is developing an adeno-associated viral vector product as a treatment for congestive heart failure, raised US\$30 M in a Series B round in 2005; and **Ceregene**, which is targeting CNS diseases, raised a similar amount (US\$32 M) in a Series B funding in 2004.

Increasing the success rate of clinical trials in this field is an obvious but imperative factor for further growth and investments. The impact of clinical failure has led many companies to reassess their involvement in only one technology or therapy area, resulting in the development of multiple technology platforms, and a consolidation in the market which awaits the licensing of products such as Advexin with impatience.

² See Feature, pages 9–10.