Gene Therapy (1997) 4, 1279–1280

Protection of patents pending

As more patents are issued for gene therapy technologies, many of the companies claiming stake to intellectual property see corporate partnerships as the route to financing costly legal battles and defending patents.

The advantage of corporate partners, with large financial reserves, is understood when the costs of legal battles for intellectual property are known. "You could spend somewhere between $200,000-300,000 a month, and this can go on for three to four years," explained **Ken Chahine**, a patent lawyer at **Madson & Metcalf** (Salt Lake City, UT, USA).

"In corporate partnerships it's built into the deal to protect the intellectual property," said **Kathleen Glaub**, senior VP and CFO of **Cell Genesys** (Foster City, CA, USA) - which, in October, received one patent for the use of adeno-associated viruses (AAV) to deliver DNA as a therapeutic agent and another for the use of lentiviral vectors.

The ability to defend intellectual property is one of the advantages of having corporate partners explained **Richard Waldron**, CFO of **GeneMedicine** (The Woodlands, TX, USA), which has "always planned to work with corporate partners". GeneMedicine received a US and European patent for the use of cationic lipids for the delivery of DNA to target cells via inhalation or injection, also in October.

Several tactics are used in the defence of patents. One of the common methods, according to Chahine, is to try and get a patent annulled. This can be done if published material, which pre-dates the patent, can be found. On these grounds the patent should not have been issued, as the information was already in the public domain.

However, there are alternatives to fighting: cross licencing of technologies allows a firm to use technology for which it has no intellectual property. Indeed, Glaub sees this as a more frequent route to acquire technology than the court room. As it is unlikely to hold the rights to all the technology it is working with, she explained, "Biotech companies will need to licence some intellectual property". For example, while Cell Genesys has a patent for AAV use, its latest research uses AAV to deliver the EPO gene to treat anaemia. Before Cell Genesys can sell any products relating to this technology it will have to get permission from **Amgen** (Thousand Oaks, CA, USA), the owner of the patent covering the use of EPO.

Several other patents were issued over the last few months including one for **Targeted Genetics** (Seattle, WA, USA) covering cationic lipids formulations. **Immune Response** (Carlsbad, CA, USA) also received a patent covering a method of stimulating an immune response against tumour cells by vaccination.

Although no legal battles have occurred in the gene therapy sector yet, in the biotechnology sector as a whole, according to Chahine, there have been more law suits filed for patent ambiguities this year and the numbers are increasing. However, the consequence, for the biotechnology company, of failure in court could be disaster. The reason for defending patents so vigorously is that they are often the difference between a firm's success and failure, Waldron explained. He added: "For GeneMedicine and other companies in the field, patents are the defining aspect [of success]."

While the gene therapy firms are developing strategies to protect their intellectual property, and consequently the business, Chahine notes that these firms are never entirely safe. "If you are a small company and have a corporate partner who loses [a law suit] and the patent is invalidated, it may be lost for all areas of use."

Gene therapy stocks not damaged in crash

While gene therapy firms were hit hard during the stock exchange tumble at the end of October it should not have any long term effects on the industry, according to analysts and the gene therapy firms.

"The gene therapy and biotech stocks are more volatile and it causes them to be hit harder. [This crash was] not specifically dangerous for the biotech sector," said **Rachel Leheny**, an analyst with **Hambrecht & Quist** (New York, NY, USA). She explained that this latest market fall and rise affected all types of businesses, but acknowledged that biotechnology firms, often have no revenues which makes their stocks more volatile and as a result are prone to greater falls than other sectors.

Daniel Geffken, CFO at **Transkaryotic Therapies** (TKT, Cambridge, MA, USA) said: "In general [when our stock price falls] I get calls enquiring what's going on. This time I got no calls." He explains this anomaly as the difference in the type of investors. "We've got two types of buyers: long term and opportunistic - [the latter] take advantage of volatility." The long term investors are the type who will query the fall in the stock market price as they want to see steady growth in the company. But, Geffken believes that these investors knew what to expect. Indeed, following TKT's drop in share price from $37 to $27 (a 37% fall) its price then rose to over $38 in less than a week following the crash.

This kind of fluctuation was seen across the whole gene therapy sector. **Vical's** (San Diego, CA, USA) stocks fell from $15.50 to $12 (a 29% fall), similarly **Alexion Pharmaceuticals** (New Haven, CT, USA) fell from $13.85 to $10.70 (a 29% fall), **Targeted Genetics** (Seattle, WA, USA) fell 33% and **Ribozyme Pharmaceuticals** (Boulder, CO, USA) was down 20%. However, all of these companies recovered within three days to around the prices before the crash.

Will stock-split save Hybridon?

Hybridon (Cambridge, MA, USA) proposed a reverse stock-split in mid-November to help maintain its position on the **Nasdaq** National Market, following threats from the stock exchange that it

would be de-listed (*Gene Therapy News* Vol 4 No 11).

Under the proposal the stock will be reverse-split where every five shares will be converted to one. As a result the firms' 25.3 million outstanding shares will be converted to approximately 5.06 million. The purpose of such action, among other factors, is to increase the share price beyond the de-listing price set by Nasdaq at $1. However, this is not Hybridon's only concern. Its rising debts are also breaching Nasdaq's listing requirements and as yet Hybridon has made no announcement on how they will tackle this.

New funds fund new trials

NeuroVir (Vancouver, Canada) raised C$9.5 million (US$6.7 million) from institutional and private investments in October. This takes its total fund raising to C$13.5 million (US$10 million) since July, which will be used to start two clinical trials, the first in early 1998 and the second later in the year.
The first of the trials is to demonstrate the safety of G207, a therapy to treat glioblastoma (malignant brain tumours) using a herpes simplex virus as the vector. The second trial will use the same type of vector to treat localised tumours outside the brain, such as head neck and lung cancers. Future trials hope to treat metastatic cancer.

RESEARCH

A team of researchers at **Cell Genesys** (Foster City, CA, USA) reported preclinical studies on its work using the erythropoietin (EPO) gene carried by an adeno-associated viral (AAV) vector as a potential treatment for anaemia. In the studies the EPO gene was successfully delivered to skeletal muscle tissue using AAV. It was shown that expression of the gene continued for more than six months following a single injection into non-dividing adult tissue. Also shown was that the levels of EPO in the blood was proportional to the dosage of the vector and gene administered. Accordingly, the results showed that red blood cell levels also increased proportionally. The research, led by **Richard Snyder**, was conducted on mice over seven months.
Human Gene Therapy Vol 8, No16

Research into a gene therapy treatment for chronic granulomatous disease (CGD) is showing positive results. CGD is caused by a defect in phagocyte NADPH oxidase (phox) which is used by the immune system to produce hydrogen peroxide to kill antigens. Mutations in one of four different genes can cause the disease which often results in infections of the skin, lungs and bones and granulomas may also be formed. Conducted by researchers at the **National Institute of Allergy and Infectious Diseases** (NIAID, Bethesda, MA, USA), the experiments took white blood stem cells from the patient, transfected them with the phox gene and returned them to the patient. The result was an increased expression of the phox gene in the white blood cells for three months after the patient received the gene-corrected stem cells. The research was conducted by **Harry Malech**.
Proceedings of the National Academy of Sciences **94**:12133-12138

Early and efficient killing of cells infected with the human immunodeficiency virus (HIV) was reported in Octobers *Proceedings of the National Academy of Science*. The work, conducted by researchers at **Cell Genesys** (Foster City, CA, USA), used genetically altered T cells, which are HIV-specific, to target HIV-infected cells and destroy them. The modified T cells are able to operate as efficiently as naturally occurring HIV-specific T cells. The research also showed that the modified T cells were able to recognise and kill various strains and mutant HIV types. The work was led by **Bruce Walker** and done in collaboration with the **Partners AIDS Research Center** (Boston, MA, USA) and **Harvard Medical School** (Boston, MA, USA).
Proceedings of the National Academy of Sciences **94**:11478-11483

A successful application of an adeno-associated viral (AAV) vector for the treatment of Parkinson's disease has been shown in animal models. The researchers used two vectors to deliver two genes, one encoding tyrosine hydroxylase (TH) and the other for L-amino acid decarboxylase (AADC). These two enzymes are precursors to the production of dopamine, which Parkinson's sufferers are short of. The results showed that rats, which had laboratory-induced Parkinson's, had significantly reduced abnormal movements following treatment with the two vectors. The research was conducted by **Avigen** (Alameda, CA, USA) in collaboration with **Jichi Medical School and Fujita Health University** (Tokyo, Japan).
27th Annual Society for Neuroscience Meeting (New Orleans, LA, USA)