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GT News

New adenoviral cancer company

A new gene therapy firm, **Cobra Therapeutics**, (Keele, UK), has surfaced through the merger of **Therexsys** (Keele, UK) and **Cobra Biosciences** (CBL, Birmingham, UK), which will focus on developing cancer therapies using adenoviral (AV) vectors. Additionally, from 1 March 1998, the firm has officially taken on **David Bloxham** as chief executive officer from his previous post at **Celltech** (Slough, UK) where he was chief operating officer.

The main reason for the merger, according to **Richard Moulson**, CFO from Therexsys and now Cobra, is that CBL, "have expertise in adenoviral [gene] delivery and we were interested in using this to deliver our gene for anticancer." According to Moulson, Therexsys was struggling to develop its cancer therapy with synthetic vectors, which was Therexsys's main vector technology.

CBL has always been affiliated to the oncology department at the **University of Birmingham** (UK) and its founders, **David Kerr**, **Lawrence Young**, and **Nigel Slater** who will have roles in the new company, have expertise in oncology and immunology. At the university, with which Cobra will maintain links, Kerr and Young have been developing AV vectors for gene therapy and have preclinical data showing *in vivo* delivery of marker genes to tumour cells strong enough to support rapid progression into clinical trials. Moulson believes the new company, "will benefit from the science being done at Birmingham University." As well as technology, CBL has one of the largest clinical trial facilities in Europe. "This is a good way for us to test our therapies," said Moulson.

The deal between the two firms consisted of Therexsys making a small cash payment to the founders of CBL and Birmingham University and issuing them with shares and options amounting to 8% of Therexsys. The new name takes on the name of the smaller firm, as Therexsys stood for therapeutic expression systems, which, according to Moulson, "related to a specific technology, but now the company is much broader."

Antisense breaks through phase III

The first antisense therapy has made it through phase III trials. Fomivirsen, for the treatment of CMV retinitis in Aids patients, is a result of a collaboration between **Isis Pharmaceuticals** (Carlsbad, CA, USA) and **Ciba Vision** (Atlanta, GA, USA). According to **Stanley Crooke**, the CEO of Isis, the company is in the process of filing a New Drug Application with the US Food and Drug Administration (Rockville, MD, USA) and fomivirsen should be on the market by the end of the year. While fomivirsen is the first of its kind to get this far, what are the future developments for antisense?

Fomivirsen has only been in development for five years, compared with up to 15 years for more conventional therapies. Additionally, the development costs were considerably lower than conventional drugs, which Crooke puts down to low scale up expenses and the ability to deliver locally, in this case to the globe of the eye by injection. When this is compared to the potential market value of the drug to Isis, which Crooke estimates at around $30 million to $60 million a year, antisense appears quite a money-spinner.

This is not the only virtue of antisense. Crooke says it is extremely safe, indeed, fomivirsen has been administered continually for two years in some patients with no side effects. Also, modifications to the chemical composition of the antisense molecules, already in trials at Isis, appear to increase stability. This, according to Crooke, will allow aerosol, rectal, and even oral delivery of antisense therapies.

However, the investment community has always been uncomfortable with antisense. "For reasons that are unclear, antisense has never had support like gene therapy," said Crooke. He feels this is caused by several factors, firstly the complexity of the field is hard to convey to investors. More significantly, there is less academic research in antisense than gene therapy. The latest example of investor disinterest in antisense is Hybridon, where continually falling share value caused it to be de-listed from the Nasdaq stock exchange (*GT News* Vol.5(2)).

To make the development on new antisense harder, Isis holds strong intellectual property covering the area. "The question for investors in antisense is 'is there enough space to work?' with out patent position," said Crooke. However, he hopes that investors will continue to take interest in Isis's competitors, as he believes this is good for the sector as a whole. "I think this is an important step in the development of antisense," concluded Crooke. However, he added, "Any single drug is not a guide to the whole sector."

Dealing in gene therapy

Several large deals between gene therapy companies occurred at the beginning of 1998 signalling continued interest in the technology with the aim of developing marketable drugs.

Firstly, in one of the largest deals seen in gene therapy, **Transgene** (Strasbourg, France) has started a collaboration with **Schering-Plough** (Madison, NJ, USA) potentially worth $88 million. The programme will use Transgene's adenoviral (AV) gene delivery vectors with Schering-Plough's p53 tumour suppresser gene.

Additionally Schering-Plough has the rights to licence Transgene's AV technology for five other genes. Initially Schering-Plough will pay Transgene $8 million, but if all six projects go ahead full payment will be made, excluding royalties on drug sales.

Also dealing with Transgene is **Human Genome Sciences** (Rockville, MD, USA). In a project set to last 10 years, Human Genome Sciences will supply up to 10 genes through its genomics programme to be used in therapies again using Transgene's AV vector delivery systems. Under the agreement, HGS will take a 10% interest in Transgene's equity, receive an initial licensing fee and funds for research. Transgene gets the right to manufacture and commercialise any products resulting from the deal. To help in the funding of this project and others, Transgene has filed with the US **Securities and Exchange Commission** (Washington, DC, USA) for an initial public offering of shares, valued at around $45 million.

Also raising money is **Copernicus Gene Systems** (Cleveland, OH, USA), which received $4.6 million through venture capital. Copernicus has just entered a collaborative research programme with **LXR Biotechnology** (Richmond, CA, USA), which specialises in apoptosis therapies. The deal will develop LXR's anticancer technology using Copernicus's DNA compaction and expression systems.

Payments from **Corange** (London, UK), the parent company of **Boehringer Mannheim** (Mannheim, Germany), were made to **GeneMedicine** (The Woodlands, TX, USA) as a result of a deal. Here GeneMedicine has received $4 million in equity investments, and will receive $1.25 million quarterly research and development payments totalling over $9 million by 2000. Boehringer Mannheim will make an additional $4 million payment in February 1999 if certain milestones are attained. The pact between Boehringer Mannheim and GeneMedicine involves the development of therapies to treat head and neck cancer and melanoma. GeneMedicine is in phase I clinical trials with its interleukin II and cationic lipid vector therapy.

EpiGenesis Pharmaceuticals (Durham, NC, USA), which focuses on the developing antisense therapies to treat asthma, has received equity financing which could amount to $5 million. The money is coming through Muzinich & Co (New York, NY, USA) which has raised $2.5 million for EpiGenesis in Europe. These funds could increase over the next two years if milestones are reached.

RESEARCH

Researchers at the **University of California** (San Diego, CA, USA) have developed a new technique for observing transgene expression using toad embryos. With inverted terminal repeats from adeno-associated virus flanking the DNA sequences of interest, genes can be inserted into embryonic stem cells by direct injection. It is as yet unclear whether the transgene is integrated with the chromosomes, but **Sylvia Evans** and her team were able to show sustained expression of the jellyfish fluorescent protein gene from egg to tadpole stage. Evans believes the technique should avoid inefficient and non-uniform gene expression.
Nature Biotechnology **16(3)**:253

A technique for hepatic gene repair without the use of viral vectors is in development at the **University of Minnesota Medical School** (Minneapolis, MN, USA). A chimeric RNA/DNA oligonucleotide was constructed to induce a sequence mutation in the rat factor IX gene, resulting in prolonged coagulation. The oligonucleotides were delivered to hepatocytes in two ways: direct *in vivo* injection and in cell cultures. According to **Clifford Steer** who headed the research, the new class of biomolecules, chimeroplasts, can be designed to target specific sites within genes and efficiently alter an animal's DNA. Also demonstrated in the research was that the chimeroplasts are not only highly specific and efficient but dose dependant.
Nature Medicine **4(3)**:285

Genes associated with psychiatric illness have been discovered by researchers at the **New York Medical College** (New York, NY, USA). **Ronnie Swift** and **Michael Swift**, who conducted the research, said that carriers of the Wolfram syndrome gene are 26 times more likely to require medical attention for depression than people without the gene. With the ability to identify genes that predispose people to psychiatric disorders, the researchers hope that doctors will be able to make more precise diagnoses and prescribe better treatments for patients.
Molecular Psychiatry **3(1)**:86-91