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GT News

Growing interest in growth factors

Vascular Endothelial Growth Factors (VEGF) are the latest focus for two gene therapy companies. **Human Genome Sciences** (Rockville, MD, USA) and **Ribozyme Pharmaceuticals** (Boulder, CO, USA) have started separate programmes to develop therapeutics using VEGF genes to treat vascular diseases and cancer. Indeed, Human Genome Sciences has established a new firm, **Vascular Genetics**, a virtual company set up with **Cato Holding** (Research Triangle Park, NC, USA), a contract research organisation, and **Jeffrey Isner**, a leading cardiologist. Isner will continue to work from the **St Elizabeth Medicinal Center** (Boston, MA, USA).

According to **William Haseltine**, chair and CEO of Human Genome Sciences, "regenerative gene therapy offers more than replacement", and this is one of the principles behind Vascular Genetics' programme. Initially, Vascular Genetics will use the VEGF-2 gene, able to activate the formation of new blood vessels, to treat limb ischemia. The therapy is to use an undisclosed vector, which is not viral, lipid or naked DNA. "We believe there are a variety of means to introduce DNA into tissues that don't rely on [traditional] technologies," explained Haseltine. Funding for the company will come from Human Genome Sciences and Cato Holdings in the form of re-payable loans. These will continue until the programme reaches phase II trials.

Human Genome Sciences, which currently owns around 20% of Vascular Genetics will have royalties on sales and has the right to buy out the other parties in the group. Cato Holdings has a 40% ownership, and **Allen Cato**, president of Cato Holdings, will be the president of the new firm. Additionally, Cato Holdings will supply a management team for Vascular Genetics. The remaining 40% ownership is equally split between Jeffrey Isner and the St Elizabeth Medicinal Center.

Simultaneously to Vascular Genetics, Ribozyme Pharmaceuticals announced a new programme using the VEGF gene to treat several cancers including lung, breast and colon, and to treat eye diseases such as age-related macular degeneration and diabetic myopathy. Ribozyme Pharmaceuticals has developed a ribozyme, called RPI.4610, which is able to destroy the mRNA responsible for the production of VEGF. The company has shown in mice with Lewis Lung carcinomas that its therapy can reduce vascularisation in tumours, resulting in inhibited tumour growth and metastasis. The programme is being run in collaboration with **Chiron** (Emeryville, CA, USA), each meeting 50% of the development costs and equally sharing the revenues on sales. Ribozyme Pharmaceuticals' funds are partially to come from a recent share offering which raised $11.2 million.

Double gene therapy improves efficacy

A new approach to increasing the efficacy of gene therapies is in development. **Megabios** (Burlingame, CA, USA) is filing an Investigational New Drug Application with the **US Food and Drug Administration** (Rockville, MD, USA) to initiate phase I trials on a therapy using two immunostimulatory genes concurrently to treat melanoma. Both the Il-2 and Superantigen-B gene will be delivered by direct injection encapsulated in a cationic lipid vector. The therapy should provoke a systemic immune response. "We can create an immune response with the Superantigen-B gene and amplify it with the Il-2," said **Benjamin McGraw**, chair, president and CEO of Megabios.

The two genes are under licence from the **National Jewish Medicinal and Research Center** (Denver, CO, USA) and the clinical trials are to be conducted at the **University of Colorado Health Sciences Center** (Denver, CO, USA) under the supervision of **Pat Walsh**. The phase I clinical trial, to start in the first half of 1998, will receive $650,000 funding from the **National Cancer Institute** (Bethesda, MD, USA) and funding beyond phase I is hoped to be met through corporate partnering. As yet Megabios has not selected a partner, but, McGraw said: "The [potential] corporate partners are impressed with the results so far." The results from pre-clinical trials, funded by Megabios and due to be published in the next few months, came from experiments conducted on dogs with oral melanoma and metastasis. However, McGraw believes that future developments of the technology could find therapies for solid tumours.

Promising clinical results

Results from a phase I/II trial on an oncology gene therapy show that the drug has potential to treat patients with advanced metastatic renal cancer. These latest trials on *Leuvectin*, owned by **Vical** (San Diego, CA, USA), used a cationic lipid vector carrying the IL-2 gene injected directly into the tumour, showed that the therapy responses appear to be dose-related and no adverse side-effects were observed even at the highest dose levels. However, according to **Alan Engbring**, a speaker for Vical, this therapy is not the main focus for the company. "We will move *Leuvectin* into phase II trials in the first half of 1998, but we are currently focusing on *Alovectin-7* for the treatment on melanoma and renal cancer," Engbring explained. The firm has around $40 million in the bank, with an research burn rate of $5-6 million a year but intends to take *Allovectin-7* to market and with the revenues help fund the development of *Leuvectin*. The firm is also considering a public offering of shares. But, if it does adopt this strategy it wants to raise enough money to take the drug to market and be able to do some small scale manufacture. Corporate partnering is also an option Engbring said: "We would be interested in some collaboration. We've had discussions with a number of [potential] corporate partners for all our products."

Further funds for antisense firm

The antisense firm **Hybridon** (Cambridge, MA, USA) intends to raise up to $50 million through private offerings of common stock. As part of the development strategy to alleviate the problems associated with its listing on the **Nasdaq** stock exchange (*Gene Therapy News* Vol 4 No 11 and Vol 4 No 12) the firm hopes to raise around $12.5 million in the first of several offerings. The money will be used for general corporate costs, preparing an investigation new drug application, clinical trials and preclinical studies. The firm anticipates 50% of the stock sales going to the US and the remaining 50% to go to the rest of the world.

RESEARCH

A project at the **University of California-San Francisco** has managed to insert a gene into the salivary glands of rats which causes the glands to produce insulin. The technique originally used naked DNA injected directly into the salivary glands. But, **Ira Goldfine**, who headed the research team, improved the delivery by using a lipid vector. However, the glands would only produce insulin for about one week following the treatment with the gene. Goldfine's team also managed to deliver genes encoding for growth hormones and believe the technique has potential use for the treatment of some cancers.
Nature Medicine Vol 3 No 12

A new gene therapy approach to treat Aids has been published by researchers at the **University of Pennsylvania**. The team, led by **Michael Endres**, took an HIV and prevented it from replicating. According to Endres the system is a gene delivery system that only targets HIV-infected cells. The researchers then inserted the gene to allow the virus to produce the CD-4 receptor and one of two genes, CCR5 or CXCR4, which encode for chemokine receptors which activate the immune system. They also added a marker gene to see if the virus had successfully infected the cells. The next stage of development according to Endres is to incorporate a gene that will actually kill off the HIV.
Science **278** (5342):1462

A new type of gene therapy vector that expresses high levels of therapeutic genes when exposed to radiative energy has been developed by researchers at the **Arizona Cancer Center** (Tucson, AZ, USA) which is sponsored by **Varian Biosynergy** (Palo Alto, CA, USA). The process, called thermoregulation, uses heat delivered by ultrasound or other medical devices to switch on locally, and control the activity of the gene therapy vectors. These types of vectors contain gene promoters that are activated and amplify the expression of the therapeutic gene when cells containing the gene are heated to a few degrees above the normal body temperature. One use for this technology, according to **Eugene Gerner** and **Evan Hersh**, team leaders, could be to enhance the effectiveness of radiation therapies.
Sixth International Conference on Gene Therapy in San Diego

A study on the use of a retroviral packaging cell line conducted by the **Fred Hutchinson Cancer Research Center** was published in December. The report showed that the PG13 cell line offers a potentially more efficient method to transfer genes into haematopoietic stem cells and possibly T-cells for use in human gene therapies. According to the study, retroviral vectors produced from PG13 were able to transduce stem cells in primates at a higher rate of efficiency than vectors produced from the PA317 cell line (which can be used to produce amphotrophic retroviral vectors). The reason for the higher efficacy is that the vectors produced by the PG13 cell line recognise a receptor which is up to five times more prevalent in human stem cells than the receptor detected by vectors from the PA317 cell line. The work, sponsored by **Targeted Genetics** (Seattle, WA, USA), was headed by **Hans-Peter Kiem** and **Dusty Miller** from the Fred Hutchinson Cancer Research Center.
Blood **90**:4638-4645

Successful long-term gene delivery to liver and muscle tissue using a lentiviral vector has been shown by researchers at the **Salk Institute** (La Jolla, CA, USA). The data from preclinical trials showed that gene expression was detected for at least six months following a single injection. In the experiments a marker gene was used to evaluate the efficacy of gene delivery to liver and muscle tissue of rodents through direct injection. No inflammation was observed during the study, suggesting that repeat administration of the vector would be possible. The programme was led by **Inder Verma** of the Salk Institute and done in conjunction with **Cell Genesys** (Foster City, CA, USA).
Nature Genetics **17**:314

Research from **Columbia University** (New York, NY, USA) may lead to a gene therapy for the treatment of sickle cell anaemia and a related disease called beta thalassemia. Using a retroviral vector the researchers delivered the β-globin gene to haemopoetic cells in the bone marrow in murine models. The presence of the gene could be detected up to eight months after transduction of the haemopoetic cells and expression of the gene was still observable in high levels. According to **Arthur Bank**, senior author of the published work, the technology could treat if not cure patients with sickle cell disease and beta thalassemia.
Blood **90**:3414-3422

A new method of gene delivery into tumours has been presented by researchers from **Kumamoto University** (Honjo, Japan) and **Genetronics Biomedical** (San Diego, CA, USA). The new technique consists of injecting the gene into a tumour and applying a very short, pulsed rotating electric field to the tumour using a special array of needles and optimised voltage and pulse length. Analysis of the tumour tissue post-treatment revealed that an extremely high percentage of the cells took up the green florescent marker gene. Other possible advantages of the method would be the ability to deliver very large genes. The work was conducted by **Toru Nishi**, from Kumamoto University and **Ken Dev** from Genetronics Biomedical.
Sixth International Conference on Gene Therapy in San Diego