Gene Therapy (1997) 4, 999–1000

Cardiovascular formation and collaboration

Three leading cardiovascular physicians have formed a new gene therapy company focusing on cardiovascular disease. **Gary Nabel**, professor of internal medicine and biological chemistry and a clinical investigator at the **University of Michigan** (Ann Arbor, MI, USA), **Elizabeth Nabel**, head of cardiology and professor of internal medicine and physiology at the University of Michigan and **Jeffrey Leiden**, the head of cardiology and professor of medicine and pathology at the **University of Chicago** (Chicago, IL, USA) will form **CardioGene's** (Princeton, NJ, USA) scientific advisory board. **Martin Cleary**, the former president and chief executive officer of **IMRE Corporation** (Seattle, WA, USA) and founding member of CardioGene, will be the president and chief executive officer of the new firm.

The founders have invested around $500,000 but, Cleary said: "To get us through the next three years...we will need $7million which we intend to get through venture capital and corporate partnering."

Another development in the cardiovascular field is a new, collaborative four-year partnership between **IntroGene** (Leiden, Netherlands) and **Flanders Interuniversity Institute** (VIB, Zwijnaarde, Belgium). Started in August, the programme will focus on the development of a gene therapy for the treatment of various cardiovascular indications. **Desiré Collen**, the head of the Center for Molecular and Vascular Biology at the **University of Leuven** (Leuven, Belgium) and the Department of Transgene Technology and Gene Therapy at VIB, will lead the project.

Using Introgene's adenoviral and adeno-associated viral vector technology, the research hopes to study the effects of three genes: ceNOS (nitric oxide synthase), PAI-I (plasminogen activator inhibitor type I) and HSV TK (HSV thymidine kinase) for the prevention of arterial restenosis. Preliminary research has shown in animals that these genes inhibit smooth muscle proliferation, which often occurs after angioplasties, and could reduce the occurrence of restinosis. Under the terms of the agreement, IntroGene will have the exclusive world rights to all commercial applications arising from the research in the fields of restenosis, arrythmia, heart failure and pulmonary hypertension.

Technology emerging through merging

CytoTherapeutics (Providence, RI, USA), which develops cell therapy systems for delivering therapeutic substances to the central nervous system, acquired **StemCells** (San Diego, CA, USA) for $7.9m of CytoTherapeutics stock in August. The new firm, which will keep the CytoTherapeutics name, will have **Richard Rose**, the former president and chief executive officer of StemCells, as its new chief executive officer and president. **Seth Rudnick**, the old chief executive officer and chair of CytoTherapeutics, will keep his position as chair.

Through the merger CytoTherapeutics now has several lines of patented technology. StemCells contributed intellectual property covering the modification, isolation and use of neural stem cells. It also has a patent for the immortalisation and de-immortalisation of neural cells. This technology inserts a modified onco-gene called *v-myc* into the neural stem cell rendering it immortal. This allows stem cells to be cultured without differentiation. A modified PCR technique can then remove the *v-myc* gene which de-immortalises the cells.

Before the merger, CytoTherapeutics held 26 issued patents and had more than 40 pending US patent applications, some of which covered delivery of living cells in encapsulating membranes. These semi-permeable membranes allow normal substances, produced by the contained living cells, to escape into the surrounding tissue without allowing the host antibodies to enter and destroy the cells. This technology is currently in phase II with **Astra** (Södertalje, Sweden) for the treatment of pain.

Acquisition of intellectual property was not the sole purpose of the merger. "The merger will mean that StemCells will remain a discovery research unit in Palo Alto for all human stem cells," explained Rose. "StemCells did not bring any financial assets to the merger, but it does have opportunities for partnership. Some of these could be realised in the near future." Rose continued by saying that money was not a major issue of the deal as CytoTherapeutics still has two years of cash reserves in the bank at the current burn-rate.

Cascading interferons upset cancers

The collaboration between **GeneMedicine** (The Woodlands, TX, USA) and **Boehringer Mannheim** (Mannheim, Germany) initiated a phase I trial in August, for a treatment for head and neck cancer at the **Johns Hopkins Institutes** (Baltimore, MD, USA). The experimental product, IL-2 Cancer Gene Medicine, is a plasmid encoding the human IL-2 gene and uses a cationic lipid vector injected directly into the tumour to transfect the cancer cells. Once in the cells the IL-2 gene causes the production of IL-12 and gamma interferon. The IL-12 also increases production of interferons which, in turn, causes an immuno-stimulation to destroy the cancerous cells.

The funding for the trials, and development of the drug, has come from Boehringer Mannheim. "To date Boehringer has supplied $13million in research funds and equity investments. And as long as the product develops on schedule funding will continue for another 2 years amounting to a further $22million," said **Richard Waldron** vice president and chief financial officer at GeneMedicine. However, a potential change in strategy may come when the drug enters phase II trials expected around mid-1998. GeneMedicine has the option to commit to sharing the funding of the drug and will take a slice of the revenue when the drug is finally sold. The alternative strategy is to leave all funding

of the drug to Boehringer Mannheim with GeneMedicine receiving royalties on sales.

According to Waldron, one of the factors that will influence the decision is the finalisation of the Boehringer Mannheim-Roche merger. "We are still unsure how the merger will affect funding. Boehringer does have rights to expand in the field and can do so from the first quarter next year," explained Waldron. However, he added that Boehringer Mannheim has no opt-out rights for the current IL-2 collaboration.

Granting grants for gag-gene

The **National Institutes of Health** (NIH, Bethesda, MD, USA) and the **University of California** (Berkeley, CA, USA) awarded **Avigen** (Alameda, CA, USA) two grants for the development of a therapy to treat HIV, in September. The Capsid Targeted Viral Inactivation is an adeno-associated virus which delivers to HIV infected cells a modified *gag* gene, which normally encodes the HIV core proteins, but has additional DNA attached which encodes for a potent nuclease. Once in the cell the modified *gag* gene replaces the normal version and is incorporated into the genome of new viruses. As the virus is constructed, the modified gene starts to produce the nuclease which breaks down the RNA in the virus preventing further replication. Although the awards received only amount to around $400,000, **John Monahan**, Avigen's chief executive officer and president said: "these are extremely competitive types of grants." He implied that the through the grants NIH is acknowledging the quality of Avigen's research. The company is not short of money. Last year it floated on the NASDAQ stock exchange and raised $22million. It is now looking for corporate partners.

Antisense of tumour trials

Phase II trials of an antisense anticancer drug started in August following positive results from phase I trials. **Isis Pharmaceuticals**' (Carlsbad, CA, USA) drug Isis3521/CGP64128A, in development with **Novartis** (Basel, Switzerland), will be tested with a variety of solid tumours including ovarian, prostate, breast, brain, colon, melanoma and lung cancers. The drug is an antisense inhibitor of protein kinase C-alpha (PKC-α) expression. PKC-α is one of a family of genes encoding transduction proteins that modulate cellular responses to environmental stimuli and is associated with the growth of a range of solid tumours.

Adam Michael

RESEARCH

Researchers at **Apotogen** (Ottawa, Ontario, Canada), the **University of Ottawa** (Ottawa, Ontario, Canada) and the **Children's Hospital of Eastern Ontario** (Ottawa, Ontario, Canada) have discovered a method to reduce brain damage caused by stroke and neuro-degenerative diseases. Delivery of a gene, encoding neuronal apoptosis inhibitory protein (NAIP), through adenovirus injection into the brain allows increased expression of the protein. This protects brain cells by inhibiting the apoptotic process. The research was lead by **George Robertson** of the University of Ottawa.
Nature Medicine **3(9)**: 997-1004

A second gene linked to p53, responsible for 60% of cancers, has been found by researchers at **Harvard Medical School** (Boston, Massachusetts, USA) and **Sanofi Recherche** (Paris, France). **Frank McKeon** from Harvard said the p73 gene could be as important as p53. The gene was found by accident while a Sanofi researcher, **Daniel Caput**, was working with cytokines. The p73 gene is positioned at the very tip of chromosome one, which is missing in many cancers.
Cell **90(4)**: 809-819

A gene improving the tracking and placing of therapeutic genes has been discovered by researchers at **St. Jude Children's Research Hospital** (Memphis, TN, USA). Green fluorescent protein (GFP), the name of the gene, can be used as a marker to assess gene transfer into bone marrow stem cells and allows identification of blood cells expressing the transferred genes *in vivo*. Consequently, researchers can view a blood sample from a living organism under a fluorescence microscope to evaluate the proportion of cells containing a transferred gene. The study was headed by **Derek Persons** and **James Allay** of St. Jude Children's Research Hospital.
Blood **90(5)**

Researchers at the **University of Chicago Medical Center** (Chicago, IL, USA) have developed an "on-off" switch for gene expression taken from a gene that is turned on only in smooth muscle cells, a key component in cardiovascular disease. The researchers were able to restrict the action of the inserted genes to a specific cell type. "The ability to direct a gene to a specific cell type and prevent expression in other cell types allows us to bypass one of the most troubling safety concerns facing gene therapy," said **Michael Parmacek** of University of Chicago Medical Center.
Journal of Clinical Investigations **100(5)**

According to researchers at **Harvard University** (Boston, MA, USA) and **Howard Hughes Medical Institute** (Boston, MA, USA) delivery of the gene encoding for dystrophin, through injection of immature muscle cells from healthy donors into the muscles of muscular dystrophy patients, has appeared to reduce muscle degeneration. Ten percent of cells injected into patients were alive six months after the delivery, and half of them had adapted into mature muscle fibres. The delivery of the gene and subsequent production of dystrophin, absent in muscular dystrophy patients, was shown using fluorescence *in situ* hybridisation, a technique that attaches a fluorescent marker to the dystrophin gene.
Nature Medicine **3(9)**: 970-977

Riku Lähteenmäki