hold no more than 20% market share. Complex market places equate to larger opportunities.

The European marketplace is also much more complex than in the US, the latter finding benefiting from a common currency, common language, common supplier base and generally larger, central research centres. In addition, the supply chain in Europe today is inefficient; several players (e.g. regional resellers) can be involved between the supplier and end-user of a product. At the same time, end-user processes are usually fragmented, with users failing to capture the right information concerning what is used and who supplies it.

Ventro aims to provide a one-stop shop solution by bringing suppliers' products together in a single searchable database with intuitive and sophisticated search capabilities. For large pharmaceutical companies, this will mean providing highly customized solutions that integrate procurement application solutions. Contract pricing with specified suppliers or the use of selected lists of suppliers will be incorporated, for example. For the rapidly expanding numbers of smaller biotechnology and start-up companies, the solution will be less customized and will remain hosted by Ventro.

There are several advantages to ordering products via such a centralized resource. Information is provided in real time, so pricing and stock availability data should be accurate. This method makes comparison of product specifications easy and enables more specialized products to be made more widely available. It is also possible to eliminate maverick purchasing – buying outside of agreed arrangements between suppliers and the company.

However, building the infrastructure to supply complete end-to-end solutions is no small undertaking. The Chemdex operation currently employs some 60 PhD qualified individuals to ensure that requirements and challenges of supplier and end-user are fully understood.

Growth strategy

Having established the technology platform, operational expertise and economies of scale, McCall believes Ventro is poised to expand rapidly in the course of the year 2000 into other marketplaces. Originally, in the US, it took 17 months and US$60 million before Chemdex achieved its first transaction. For example, the first transaction for the second venture, Promedix – focusing on speciality medical products and services – took place after only four months. Expansion into new marketplaces is expected to be even more rapid. At present, Ventro operate in four industry-specific marketplaces, but by year end, they expect to be operating in a further six.

David Hughes

Gene therapy alternative to HAART for HIV

HIV infection could be treated using gene therapy in the future, to inhibit activation of the latent virus. A team based at The Children's Hospital of Philadelphia (PA, USA) has shown that inserting the *antitat* gene into blood cells from infected patients can inhibit the replication of HIV-1 (Ref. 1).

The prognosis for infected individuals has improved over the past few years with the introduction of highly active antiretroviral therapy (HAART), a combination of drugs that decreases HIV replication to undetectable levels in many patients, confining the virus to a latent state. However, HAART presents serious problems. Treatment is expensive, difficult to follow and might have to be taken for life, and the side effects include loss of appetite and increased vulnerability to other infections. Recent studies have shown that latent HIV-1 infection persists in the $CD4^+$ T lymphocytes even in HAART patients with well-controlled viral replication, and these cells decay very slowly[2]. If treatment with HAART is discontinued, the reservoir of latent virus can re-emerge as an active infection[3].

Involvement of TAT in HIV

A viral protein called TAT is a key target for any potential genetic intervention in HIV replication. Produced by the *tat* gene, TAT is involved in the expression of all HIV genes by interacting with a viral RNA sequence called the *tat* activation response element (TAR)[4]. It is also involved in the pathogenesis of AIDS by activating the expression of inflammatory cytokines, some of which (e.g. TNFα) are promoters of HIV replication[5]. TAT is therefore essential for HIV-1 replication and important in the transition from latent to active infection[1].

The Philadelphia team used an artificially designed antisense gene called *antitat* to inhibit TAT. Antisense molecules are RNA strands that bind to complementary mRNA from the target

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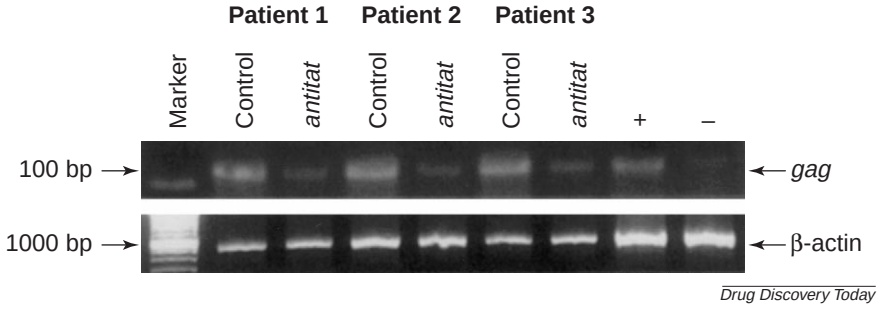

Figure 1. *RT-PCR analysis showing inhibition of HIV-1 gag gene expression in peripheral blood mononuclear cells taken from patients infected with HIV-1. Expression of the gene was induced with TNFα and PMA 24 h before analysis. Abbreviation: bp, base pairs.*

gene, thus preventing its translation into a protein. *Antitat* is a dual-function gene: as well as inhibiting the formation of TAT by binding to the *tat* gene's mRNA, it causes polymeric TAR to bind to TAT and sequesters it in the nucleus[4]. Conveniently from a therapeutic point of view, *antitat* is only expressed after activation by TAT, so expression should be confined to cells in which TAT, and therefore HIV, is present. Furthermore, as it is made from RNA, *antitat* is unlikely to provoke an immune response in the way that a foreign protein might.

Effects of *antitat*

In the first phase of the study[1], *antitat* was inserted into chronically HIV-infected U1 promonocytic cells and ACH-2 T-lymphocytes, widely used *in vitro* models for viral latency, using a mouse retroviral vector. In both cell lines, HIV-1 replication can be induced using TNFα and PMA (phorbol 12-myristate 13-acetate). Control groups of cells were transduced with a control vector, and all were then incubated with TNFα and PMA. HIV-1 gene expression was measured using RT-PCR to detect the HIV-1 *gag* gene. *Antitat*-treated cells from both lines proved highly resistant to HIV-1 expression compared with controls, even after maintenance of the cultures for a further five months. This suggests that the *antitat* gene remains functional for many months and is passed on to the progeny when cells divide.

The team then examined the effect of *antitat* in mononuclear cells from the blood of HIV-infected patients. Again, HIV-1 *gag* gene expression was inhibited, indicating inhibition of viral replication[1] (Fig. 1). This finding is particularly important as it suggests that *antitat* could be effective in humans *in vivo*. *Antitat* also increased $CD4^+$ T lymphocyte proliferation when cells from infected blood were cultured, highlighting a potential way of rebuilding the immune system in AIDS patients. 'Loss of CD4 cells is thought to be the major mechanism by which HIV-infected individuals develop immunodeficiency', said coauthor Stuart Starr, 'so preservation of these cells should prevent or reverse immunodeficiency.'

Future studies

These results confirm that *antitat* gene therapy is a promising approach for controlling viral replication in HIV. According to Starr, 'The *antitat* gene offers the possibility of prolonging the latency period indefinitely, without the need for long-term antiretroviral treatment. Early indications are that it does not affect uninfected cells or cause toxic side effects.'

The next step will be to test *antitat* gene therapy in an animal model of HIV infection. However, transduction efficiency is currently low, and random integration of the vector into the cellular DNA could mean that *antitat* is not expressed in all the cells it enters. Hence, the biggest challenge, whether in animals or humans, will be to introduce the gene into enough CD4 cells to be effective.

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