Rapid progress in genetic research has created excitement and expectations that gene-based therapies will revolutionize medical care. Among the promising therapeutic approaches is antisense technology – oligonucleotides (molecules structurally similar to DNA) designed to be complementary to a target RNA sequence so they will bind to the target and stop the production of undesirable proteins. This gene selectivity promises to enable more targeted drug design and produce more effective and less toxic therapeutics. The world’s first and only antisense drug approved by the Food and Drug Administration is Vitravene™, an oligonucleotide that treats cytomegalovirus retinitis (CMV-R) in persons with AIDS.

Vitravene™ therapy, developed by Isis Pharmaceuticals, Inc., involves periodic localized injection into the infected eye. It binds to a sequence of CMV mRNA from which proteins essential for CMV replication are made. The resulting double-stranded complex is recognized by RNase H, an enzyme that destroys the mRNA but leaves the Vitravene™ intact and active. This targeted antisense mechanism, plus the fact that Vitravene™ is not absorbed from the eye into the body, reduces the chance of drug interactions and cross-resistance with the array of other drugs used to treat persons with HIV.

**Epidemiology of CMV-R: The Target Recedes**

Cytomegalovirus (CMV) is a common virus in the herpes family, typically requiring no treatment. In people with severely impaired immune systems, however, CMV is a dangerous pathogen that may invade any organ. In people with AIDS, the most common manifestation of CMV infection is retinitis (CMV-R), inflammation of the retina of the eye. CMV-R is among the most common AIDS-associated illnesses. It is a late-stage AIDS infection, associated with CD4+T cell counts below 50 cells/mcl. CMV-R causes lesions that progressively destroy the retina. Untreated CMV-R generally causes blindness within six months. Immune recovery stops disease progression, but does not restore the parts of the retina that may have already been destroyed. There is no cure; anti-CMV treatment can control the disease process, but visual loss will resume if the patient develops resistance to or cannot continue treatment.

By the early 1990s, when ISIS was deciding which potential antisense targets to pursue, AIDS had transformed CMV-R from a rare disease into one of the most common ocular infections in the United States. Vitravene was aimed at this significant public health problem.

During the short time that Vitravene was in Phase III clinical trials, antiviral therapies strong enough to contain HIV infection in many people were developed. These Highly Active Anti-retroviral Therapy (HAART) regimens suppress HIV replication and allow the immune system to recover. As a consequence of immune recovery with HAART and the dramatic reduction in the number of HIV patients with low CD4+T counts, the number of new cases of CMV-R declined by 55-75%. When Vitravene™ came to market, HAART had been standard therapy for about a year. New cases of CMV-R were less common, and many existing cases no longer needed treatment -- the health crisis that Vitravene™ was designed to address had receded. HAART had transformed CMV-R into a condition seen primarily in patients who have been unable to tolerate or who have become resistant to HAART.

**Management of CMV-R**

Active CMV-R infection requires immediate treatment. When a CMV lesion develops in one eye, there is a significant chance that CMV infection will appear in the other eye (50%) or elsewhere in the body (31%) in the next several months. For this reason, systemic therapy is often the treatment of choice. Local therapy may be added if the lesion is immediately threatening vision. Immune recovery with HAART halts progression of CMV-R lesions, and allows many patients to stop CMV-R specific treatment.

Today, the most frequent treatments for CMV-R are surgical placement of a ganciclovir implant into the affected eye and oral valganciclovir. These are often combined to control eye disease and prevent spread of the virus. Other available therapies include intravenous ganciclovir, foscarnet, and cidovir. Resistance to these drugs often develops within 3 to 6 months.
Vitravene™ offers an alternative for patients in whom other local treatments are no longer effective or are contraindicated. It produces a “prolonged and durable response” in refractory disease, significantly delaying disease progression in a majority of patients. Vitravene™ can delay progression of CMV-R for over a year.

**Development of Vitravene®**

**Role of NIH and FDA**

The array of innovations required for the development of Vitravene™ by ISIS Pharmaceuticals includes two inventions licensed to ISIS from HHS. A team of scientists at the National Cancer Institute (Drs. Jack S. Cohen, Len Neckers, Cy Stein, She L. Loke, and Kazuo Shinozuka) discovered that using phosphorothioate (sulphur substituted) oligonucleotides as DNA backbones for antisense construction results in effective antiviral compounds that are more stable in human cells. They also reach a greater variety of cells than other types of oligonucleotides and bind to complementary RNA sequences more efficiently. Automation is essential to producing the quantities of oligonucleotides necessary to develop drugs from these compounds. Drs. Serge Beaucage, Judith B. Regan, and Radhakrishnan P. Iyer at the FDA discovered a novel sulfurization method that overcame a major barrier to the reliable, high yield automated synthesis of phosphorothioated oligonucleotides.

At the time these licenses were negotiated, the field of phosphorothioate oligonucleotide antisense technology was in its infancy, and potentially useful for a vast array of drug products and research tools. A key role for the NIH Office of Technology Transfer (OTT) and its predecessor office was therefore to ensure that these technologies were broadly available for the commercial development of any potential therapeutic. OTT denied requests for exclusive licenses and negotiated nonexclusive agreements with several companies.

**Role of Isis Pharmaceuticals**

ISIS undertook the extensive effort necessary to develop this drug and prove the therapeutic potential of this class of molecules. ISIS synthesized thousands of antisense molecules, and identified those with potential therapeutic activity. ISIS performed all pre-clinical work, developed the intravitreal formulation, and conducted all the clinical trials. In addition, antisense molecules had never before been tested or manufactured for use as pharmaceuticals; ISIS developed new animal models and new manufacturing and analysis methods necessary for this novel type of drug.

This pioneering work demonstrated that antisense drugs could meet the regulatory criteria of the FDA, and laid to rest many concerns about whether antisense technology could be manufactured for commercial use. ISIS also met an ambitious milestone timetable, and brought Vitravene™ to market ahead of schedule. In 2000, Vitravene™ received a Galenus Prize for pharmaceutical innovation.

**Public Health Benefits**

As ‘proof of concept’ for the commercialization of antisense pharmaceuticals, Vitravene™ was a major breakthrough. In addition, the scientific and drug development innovations made by the NIH, FDA, and ISIS laid the groundwork for the new generation of antisense compounds now being tested for a wide array of potential indications. But Vitravene™ is more than a scientific pioneer. For the patients who receive it, Vitravene™ delays the progression of this frightening disease. It provides both hope and extra months of sight when other therapies have failed.

**References**


6. The Galenus Prize is awarded to the most innovative therapies approved in Europe each year. In 2000, the Galenus panel (European medical and pharmaceutical experts) selected Vitravene as the second-leading innovative therapy.

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