



Combating HIV and Hepatitis C Viral Diseases: Roche Palo Alto Virology Backgrounder

The impact of viruses is a growing medical concern. These tiny parasites have long helped shape the course of human evolution and in some cases have likely become embedded in genes and in the structure of parts of cells. As the human population has grown, viral diseases have gained an increasing foothold – spurred by the increased proximity of human populations and migration into new areas. In addition, some viruses have begun to cross species barriers (i.e., from monkeys to humans) and propagate in explosive ways. While concentrated vaccination efforts have resulted in eradication of a few viral diseases, including polio and smallpox, many viruses still remain a major challenge for public health. In addition, medical professionals and researchers are now struggling to address the rapid emergence, or re-emergence, and spread of virulent new viral diseases such as West Nile, Ebola and severe acute respiratory syndrome (SARS).

As the number and impact of new viral diseases such as HIV began increasing exponentially in the late 1980s, the international Roche Group became committed to virology research. Motivated by obvious unmet medical need and increasing knowledge about specific viral diseases, Roche launched aggressive therapeutic and diagnostic viral research programs targeted primarily at two of the most widespread, life threatening and challenging viral diseases: human immunodeficiency virus (HIV) and hepatitis C virus (HCV).

Today Roche has a strong viral diseases research group that can cite among its accomplishments since 1986 the development of two first-in-class drugs for the treatment of HIV (protease inhibitor Invirase[®] and fusion inhibitor Fuzeon[™]), and the development of an improved formulation of interferon called pegylated interferon – a standard therapy when combined with ribavirin for adults with hepatitis C (Pegasys[®]). Based out of the Roche Palo Alto facility, the group maintains an aggressive research program that promises a continued stream of new weapons in the battle against viral diseases. In particular, the Roche viral diseases research group is now focused on improving existing therapies for HIV and HCV to make them both more effective and tolerable – and thereby improving patient adherence to treatment and treatment outcomes. In addition, the group works increasingly closely with the Roche Diagnostics division to marry pharmaceutical and diagnostics expertise into advanced research intended to identify and target the genomic factors associated with viral disease, drug resistance and individual variation in therapeutic response.

Roche's Commitment to HIV/AIDS

Since 1982, when scientists identified and named the human immunodeficiency virus, researchers have struggled to find solutions to the disease. Nucleoside analogs were among the first compounds shown to be effective against HIV infection. Early therapies in this class of medicines, including AZT, ddT and Roche's own HIVID[®] – a nucleoside reverse transcriptase inhibitor which became available in 1992 – provided some benefit to patients but proved to have limited efficacy and significant toxicities.

Companies have since introduced a total of 20 anti-HIV/AIDS drugs in four separate classes: reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and the new class of medicines, fusion inhibitors, the first of which is Fuzeon, developed by Roche in partnership with Trimeris and approved by the FDA in March 2003. However, as scientists have worked to provide new options, HIV is surviving and thriving: worldwide, about 42 million people are now living with HIV or AIDS, 2.7 million of whom are children under the age of 15.

Working to Develop a Broad Range of Options for Patients

Medical professionals, patients and scientists have now re-set expectations for the treatment of HIV: it seems best to acknowledge that a cure will continue to be elusive – at least in the near-term. Many now consider it possible to address HIV as a chronic disease – one that, with adequate therapy, can be controlled for the normal lifespan of patients. The goal for scientists at Roche is to help create the broadest possible range of options for patients – i.e., to develop therapies that will effectively address patients' individual variations in disease type, viral mutations and therapeutic response.

One example of this type of therapy is Fuzeon, developed for the treatment of HIV-1 infection in treatment-experienced patients in whom HIV continues to replicate despite ongoing antiretroviral therapy. Unlike all currently approved anti-HIV drugs, Fuzeon blocks the virus from entering the human immune cell. One of the most complex molecules ever chemically-manufactured on a large scale by the pharmaceutical industry, Fuzeon provides significant therapeutic benefit with minimal side effects. Fuzeon represents the first new class of treatments in seven years. As a novel treatment option – and one that has demonstrated ability to help patients who no longer benefit from other available therapies – Fuzeon was anxiously awaited and eagerly adopted by medical professionals and patients.

“Because of its complexity, Fuzeon required Roche to take a tremendous risk in development and production – but we saw the desperate need for this compound and were determined to develop it,” said Nick Cammack, Ph.D., head of Viral Diseases Research at Roche Palo Alto. “Despite the growing range of therapies available to treat HIV and AIDS, there will always be a segment of patients who need more options. Our goal is to help ensure patients have these options. In the future we expect to bring forward more potent fusion inhibitors through our collaboration with Trimeris.”

To continue building on the portfolio of available anti-HIV therapies, Roche's viral diseases group is currently conducting research to identify new compounds within three of the four existing classes of HIV therapies (i.e., non-nucleoside reverse transcriptase inhibitors, protease inhibitors and fusion inhibitors).

Creating New Medicines to Target Resistant HIV Strains

One of the most challenging problems associated with HIV/AIDS is the increasing presence of drug-resistant HIV strains – primarily in patients who have received extensive therapy, but also among those who are newly infected. Roche scientists are working to create compounds that will target these mutant HIV strains.

Roche's viral diseases research team has already identified several new protease inhibitor drug candidates that may work against viruses resistant to available medicines in this class. The leading compound among these candidates is R944, which has demonstrated potent anti-viral activity against both wild-type and protease inhibitor-resistant HIV tested in the laboratory.

Fighting Opportunistic Infections with Adjunct Therapies

Roche is also committed to the discovery and development of adjunct therapies to fight opportunistic HIV infections. In 1989, Roche's Cytovene® (ganciclovir), was approved as an intravenous therapy for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. CMV retinitis, which can lead to blindness, affects between 10 and 15 percent of people with late-stage HIV disease. To improve patient convenience, Roche sought to make further improvements to ganciclovir or to identify a prodrug that could be used as an oral induction treatment. Following a detailed investigation of many potential prodrug strategies, Roche discovered and developed Valcyte™ (valganciclovir), which was approved by the FDA in 2001 for treatment of CMV retinitis.

Roche's Battle Against Hepatitis C

The battle against hepatitis C virus (HCV) is a fairly new one: hepatitis C was first identified and named in 1989. HCV currently affects approximately 170 million individuals worldwide, making it more common than the HIV virus. Chronic HCV is the most common reason for liver transplants and is one of the leading causes of liver fibrosis and cirrhosis. The Centers for Disease Control and Prevention expect the number of hospitalizations and deaths from complications of the disease to triple within 15 years, due to increases in the number of symptomatic patients, as well as aggressive public and professional education programs, which will lead more people to seek diagnosis and treatment.

There are numerous challenges associated with the treatment of HCV. First, the virus mutates rapidly; there are six major genotypes of HCV and within these, at least 50 subtypes of the virus. Treatment for this disease has evolved rapidly since 1989, when conventional interferon was used that overall, had limited efficacy in only up to 19 percent of patients; involved a three-times-per-week injection and was associated with numerous side effects. Pegylated interferon and ribavirin is the standard therapy for HCV (NIH consensus conference on the management of HCV, 2002). One of the major advances in the development of pegylated interferons has been the increase seen in efficacy. Whereas historically only about 7 percent of patients with genotype 1 virus – the dominant virus in many countries including the United State, Japan and Europe – were able to clear the HCV virus, today, approximately 50 percent of these patients can successfully clear the virus with PEGASYS and Copegus (ribavirin, USP).

Improving the Standard of Care for HCV Patients

To address the significant unmet need in HCV therapy Roche's viral diseases research group created Pegasys[®], a pegylated interferon that remains active in the bloodstream over a one-week period and at a more constant level than interferon alpha. The U.S. FDA approved Pegasys monotherapy in October 2002 and combination therapy with Copegus in December 2002, for the treatment of adults with chronic hepatitis C virus who have compensated liver disease and have not previously been treated with interferon alpha.

However, long-term improvement in HCV occurs only if HCV RNA disappears during therapy and stays undetectable once therapy is stopped.”¹

The Roche viral diseases research group is working to improve upon the standard of care – both in terms of efficacy and tolerability. In addition, Roche acquired and is testing the immunomodulator levovirin, a potential alternative to ribavirin.

Finally, the company is looking at other antivirals that could enhance the effect of Pegasys and ribavirin/levovirin, including one or two early first-generation polymerases or protease inhibitors to be developed by the Roche viral diseases research group or in-licensed.

“Pegasys is a significant step forward in the treatment of HCV and we are pleased to have made it available to patients, said Cammack. “However, there is still a need for drugs that are even more effective and better tolerated.” Roche is looking to strategic alliances as one strategy to compliment internal research and development in the pursuit of novel medicines. Roche recently entered into a collaboration with Maxygen which includes the development and commercialization of Maxygen's next-generation interferon alpha and beta product candidates for hepatitis C.

Combining Disease and Assay Knowledge to Tailor Anti-Viral Therapy

Roche Molecular Diagnostics, one of five Roche Diagnostics business areas, is responsible for several pioneering steps in the diagnosis of viral diseases including HIV and HCV. This Roche business was the first to translate polymerase chain reaction (PCR) technology into commercial products for routine use.

PCR enables much more sensitive detection of these diseases in blood – meaning that PCR can identify HIV and HCV earlier and in much smaller quantities than older technologies. The availability of PCR testing represented a significant advance in the diagnosis and monitoring of viral diseases. PCR is now used routinely not only to diagnose HIV and HCV as soon as possible, but to measure virus levels in the blood, thereby monitoring disease progression and/or therapeutic response at multiple points during the course of patient care.

This year, Roche Molecular Diagnostics will introduce the company's two new, real-time PCR tests, the TaqMan[™] HIV Analyte Specific Reagent and the TaqMan[™] HCV Analyte Specific Reagent, which are more sensitive and have a broader dynamic range than other available in-vitro diagnostic tests. Roche TaqMan instruments and test kits also offer laboratories improved ease-of-use, making this improved technology available to laboratories that formerly were not able to perform PCR

testing. The company is also adding HIV and HCV genotyping to its product portfolio in order to offer comprehensive disease management solutions to patients being treated for HIV and HCV.

Now, by integrating the expertise of the Roche viral diseases Pharmaceutical research and Diagnostics businesses, the company is tackling another important element of antiviral therapy: tailoring disease management based on an individual patient's genetic predictors of response, or non-response, to therapy and rate of disease progression, in addition to the specific characteristics of the virus they harbor. Treatment success rates can be greatly enhanced and unnecessary side effects reduced by the ability to precisely identify a patient's type of viral disease, existing markers for drug resistance, potential for response to therapy, and the effectiveness of a selected therapy early in treatment. For example, Roche is pursuing the development of molecular tests that will help identify HCV patients unlikely to respond to interferon, thereby sparing those patients the side effects associated with this drug and pointing their physicians to alternative therapeutic directions more quickly.

Gaining Ground on Challenging Diseases

Viral diseases present daunting challenges worldwide in terms of scope, disease variation and evolution. Roche has created an advanced portfolio of products to address some of the most challenging viral diseases, including HCV and HIV. Roche is committed to continually improve upon existing therapies and disease management protocols to make treatment for these challenging diseases both more effective and more tolerable for patients.

About Roche

Headquartered in Basel, Switzerland, Roche is one of the world's leading innovation-driven healthcare groups. Its core businesses are pharmaceuticals and diagnostics. Roche is number one in the global diagnostics market, the leading supplier of pharmaceuticals for cancer and a leader in virology and transplantation. As a supplier of products and services for the prevention, diagnosis and treatment of disease, the Group contributes on a broad range of fronts to improving people's health and quality of life. Roche employs approximately 65,000 people in 150 countries. The Group has alliances and research and development agreements with numerous partners, including majority ownership interests in Genentech and Chugai.

The 1,000 women and men at the Roche Palo Alto research and development center in Palo Alto, Calif., are focused on the discovery and early clinical development of innovative medicines to treat diseases in the following areas: arthritis, asthma and other respiratory diseases; Alzheimer's disease, anxiety, depression, schizophrenia and other diseases of the central nervous system; genitourinary diseases, HIV/AIDS, and hepatitis C.

Following are URLs for Roche on the web:

Global website: www.roche.com.

U.S. pharmaceuticals business: www.rocheusa.com.

Roche Palo Alto: <http://paloalto.roche.com>.

Roche Molecular Diagnostics: <http://www.roche-diagnostics.com>

Pegasys Product Information

Alpha interferons, including Pegasys, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping Pegasys therapy (see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE EVENTS in complete product information).

Use with Ribavirin. Ribavirin, including Copegus may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease. Ribavirin is genotoxic, mutagenic, and should be considered a potential carcinogen (see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and ADVERSE EVENTS in complete product information).

Pegasys is contraindicated in patients with hypersensitivity to Pegasys or any of its components, autoimmune hepatitis, and decompensated hepatic disease (Child-Pugh class B and C) before or during treatment with Pegasys. Pegasys is also contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal. Pegasys and Copegus therapy is additionally contraindicated in patients with a hypersensitivity to Copegus or any of its components, women who are pregnant, men whose female partners are pregnant, and patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

COPEGUS THERAPY SHOULD NOT BE STARTED UNLESS A REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY PRIOR TO INITIATION OF THERAPY. Women of childbearing potential and men must use two forms of effective contraception during treatment and during the six months after treatment has concluded. Routine monthly pregnancy test must be performed during this time. If pregnancy should occur during treatment or during six months post-therapy, the patient must be advised of the significant teratogenic risk of Copegus therapy to the fetus. Physicians and patients are strongly encouraged to report any pregnancies that do occur to Roche by calling 1-800-526-6367.

The most common adverse events reported for Pegasys and Copegus combination therapy, observed in clinical trials (n=451), were fatigue/asthenia (65%), headache (43%), pyrexia (41%), myalgia (40%), irritability/anxiety/nervousness (33%), insomnia (30%), alopecia (28%), neutropenia (27%), nausea/vomiting (25%), rigors (25%), anorexia (24%), injection site reaction (23%), arthralgia (22%), depression (20%), pruritus (19%) and dermatitis (16%).

Serious adverse events include neuropsychiatric disorders (suicidal ideation and suicide attempt), serious and severe bacterial infections, bone marrow toxicity (cytopenia and rarely, aplastic anemia), cardiovascular disorders (hypertension, arrhythmias and myocardial infarction), hypersensitivity (including anaphylaxis), endocrine disorders (including thyroid disorders and diabetes mellitus), autoimmune disorders (including psoriasis and lupus), pulmonary disorders (dyspnea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and Hemorrhagic/ischemiccolitis), pancreatitis, and ophthalmologic disorders (decrease or loss of vision, retinopathy including macular edema and retinal thrombosis/hemorrhages, optic neuritis and papilledema).

The complete package inserts for Pegasys and Copegus are available at www.pegasys.com, or by calling 1-877-PEGASYS.

FUZEON Indication and Safety

FUZEON in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of FUZEON of 24 weeks' duration. Subjects enrolled were treatment-experienced adults; many had advanced disease. There are no studies of FUZEON in antiretroviral naive patients. There are no results from controlled trials evaluating the effect of FUZEON on clinical progression of HIV-1.

FUZEON is administered as a twice-daily subcutaneous injection. Injection site reactions are the most common adverse events associated with FUZEON. Injection site reactions occurred in 98% of patients studied and 3% discontinued

FUZEON due to injection site reactions. Signs/symptoms may include pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Nine percent of patients had local reactions that required analgesics or limited usual activities.

There was less than five percent difference in the most common adverse events seen between FUZEON plus an individualized regimen of antiretroviral drugs and an individualized regimen alone at 24 weeks. The events most frequently reported in subjects receiving FUZEON plus an individualized regimen were diarrhea (26.8%), nausea (20.1%), and fatigue (16.1%). All these events were seen at a lower incidence than in subjects that received background regimen alone: diarrhea (33.5%), nausea (23.7%), and fatigue (17.4%). The most common adverse events seen more frequently in patients receiving FUZEON plus an individualized regimen than in patients who received treatment without FUZEON include headache (11.8%), peripheral neuropathy (8.9%), dizziness (6.6%), insomnia (11.3%), depression (8.6%), decreased appetite (6.3%), asthenia (5.7%), myalgia (5.0%), constipation (3.9%) and pancreatitis (2.4%). The majority of adverse events were of mild or moderate intensity.

Hypersensitivity reactions have been associated with FUZEON therapy (less than or equal to 1 percent) and have recurred on rechallenge. Symptoms of an allergic reaction may include rash, fever, nausea and vomiting, chills, rigors, hypotension, and elevated serum transaminases.

An increased rate of bacterial pneumonia was observed in patients treated with FUZEON in the Phase III clinical trials compared to the control arm. It is unclear if the increased incidence of pneumonia is related to FUZEON use.

Patients taking FUZEON may acquire opportunistic infections or other conditions that are associated with HIV infection. The list of side effects is not complete at this time because FUZEON is still being studied.

FUZEON does not cure HIV infection or AIDS. FUZEON does not reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should continue to practice safer sex by using latex or polyurethane condoms or other barrier methods. Never use or share dirty needles.

¹ www.niddk.nih.gov/health/digest/pubs/chrnhepc/chrnhepc.htm