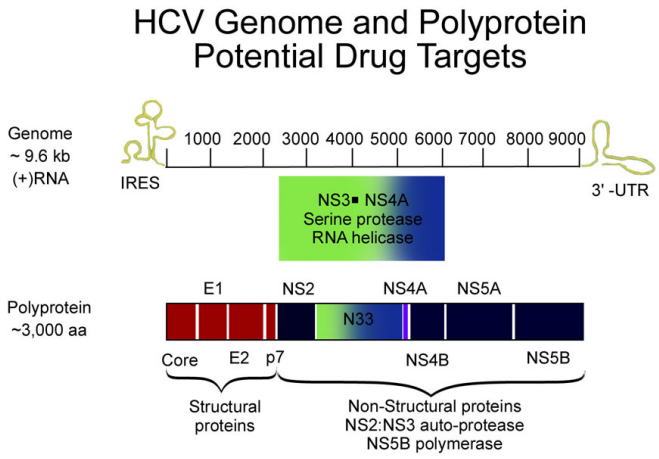
Hepatitis C

Introduction

An estimated 3% of the world's population — more than 170 million people — are infected with the hepatitis C virus (HCV). Most infections become chronic. Chronic infection is a condition that is incurable in many patients, leading to cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC). Current therapy for chronic hepatitis C includes pegylated interferon and ribavirin. The goal of therapy is to slow or halt progression of liver fibrosis and prevent the development of cirrhosis. Our understanding of HCV, and how to treat it, is growing rapidly. Multidrug regimens using new therapies in combination with existing medications have raised the level of hope for the future for millions of patients worldwide. These medical advances are only the beginning of a new era of HCV therapy.

HCV

HCV is a spherical, enveloped, single-stranded RNA virus. HCV has a rapid replication rate and can produce more than 10 trillion new viral particles each day. The HCV genome consists of approximately 9500 base pairs and encodes a single polyprotein of 3011 amino acids that are processed into 10 structural and regulatory proteins (see the image below).



The nonstructural components of HCV include NS2, NS3, NS4A, NS4B, NS5A, NS5B, and p7. These enzymes are critical in viral replication and are attractive targets for antiviral therapy.

Six major HCV genotypes, designated by the numbers 1 through 6, and numerous subtypes (e.g., 1a, 1b, 2a, etc.) have been identified. Molecular differences between genotypes are relatively large, with a difference of at least 30% at the nucleotide level.

The major HCV genotype worldwide is genotype 1, which accounts for 40-80% of all isolates. Genotypes 1a and 1b are prevalent in the United States (approximately 70-75% of patients), whereas in other countries, genotype 1a is less frequent. Genotypes 2 and 3 are also found globally but account for a significant minority of infections. HCV genotype 1, particularly 1b, does not respond to therapy as well as genotypes 2 and 3. Genotype 1 may be associated with more severe liver disease and a higher risk of HCC.

Current Therapy

Treatment for chronic HCV infection is a fairly new development. Therapy for chronic hepatitis C infection became first available in 1991, with the US Food and Drug Administration's (FDA) approval of interferon alpha. This is a genetically engineered synthetic interferon designed to mimic the body's natural interferon. Even though scientists do not understand completely how interferons work, they believe that one of their functions is to interfere with viral replication, the production of new viruses. At the beginning of the twentieth century, there was another advance in HCV treatment. By adding ribavirin (RBV) to interferon, treatment success rates improved. Although not fully understood, ribavirin weakens HCV, making it multiply less readily. RBV must be used with interferon in order to be effective. The most significant HCV treatment advance occurred in 2001, with the approval of pegylated interferon (Peg-IFN). Pegylation is a process that uses polyethylene glycol to coat a protein in order to strengthen and extend its activity in the body. The use of Peg-IFN plus RBV boosted treatment success rates to roughly 50%.

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Clinical Research

The goals of treatment of chronic HCV infection are to (1) achieve sustained eradication of HCV (i.e., sustained virologic response [SVR]), defined as the persistent absence of HCV RNA in serum 6 months or more after completing antiviral treatment, and (2) prevent progression to cirrhosis, HCC, and decompensated liver disease requiring liver transplantation.

Despite the advent of new treatment strategies with the addition of ribavirin to PEG-IFN, current available therapies for chronic HCV infection are effective only in approximately 50% of patients with HCV genotype 1. The addition of telaprevir, a protease inhibitor with the ability to block HCV replication by inhibiting a key viral enzyme (NS3-4A serine protease) to the current treatment regimen significantly improved SVR in patients with genotype 1 HCV; similar results have been achieved with another protease inhibitor, boceprevir.

Protease inhibitors used in conjunction with pegylated interferon and ribavirin are becoming the new standard of care for the treatment of chronic HCV infection. The US FDA has approved boceprevir and telaprevir for chronic HCV infection, making it the first new drugs sanctioned for use against HCV in the last 10 years. Boceprevir and telaprevir are approved for the treatment of chronic hepatitis C genotype 1 infection, in combination with PEG-IFN and RBV. These new treatments effectively doubled the sustained virologic response rate, from about 20% to 40% with the standard of care to, in some cases, more than 60% with added boceprevir and telaprevir.

Although these multidrug regimens are complex and drug resistance can develop, these developments are regarded as the beginning of a new era in the treatment of patients with hepatitis C. Some examples of drug candidates and HCV targeting strategies currently under clinical investigation are listed below:

Pharmacological Activity	Drug Candidates	Companies
NS4B Inhibitor	Clemizole	Eiger
Entry Inhibitor	ITX-5061	iTherX
NS5A Inhibitor	AZD-7295; BMS-824383; BMS 790052; PPI-461	AstraZeneca; Bristol-Myers Squibb; Presidio
NS5B Polymerase Inhibitor	ABT-072; ABT-333; IDX375; INX-189; MK-3281; PSI-7977; PSI-938; TMC649128; VX-916; VX-222; VX-759; ANA598; BI 207127; BMS 791325; Filibuvir; Tegobuvir; Mericitabine	Abbott; Idenix; Inhibitex; Merck; Pharmasset; Medivir; Tibotec; Vertex; Anadys; Boehringer Ingelheim; Bristol-Myers Squibb; Pfizer; Gilead; Roche
NS3-4A Protease Inhibitor	BIT225; VX-500; ABT-450; BMS 650032; GS-9256; Danoprevir; Vaniprevir; Boceprivir; BI 201335; Telaprevir; TMC435	Biotron; Vertex; Abbott; Enanta; Achillion; Bristol-Myers Squibb; Gilead; InterMune; Roche; Merck; Boehringer Ingelheim; Medivir; Tibotec

References

Hepatitis C virus resistance to protease inhibitors, Journal of Hepatology, DOI: 10.1016/j.jhep.2011.01.011.

A New Era of Hepatitis C Therapy Begins, N Engl J Med 2011; 364:1272 - 1274.

Boceprevir for Untreated Chronic HCV Genotype 1 Infection, N Engl J Med 2011; 364:1195-1206.

Telaprevir and Peginterferon with or without Ribavirin for Chronic HCV Infection, N Engl J Med 2009; 360:1839 – 1850.

Nature Insight: Hepatitis C, Nature 2005; 436: 929 – 978

QPS is committed to working with you

QPS has extensive experience in supporting HCV therapeutic product development for many companies. We understand the complexities, particularly with respect to managing and conducting (global) clinical trials, and monitoring the pharmacokinetics of your new drug candidates in combination with pegylated interferon and ribavirin. We are committed to working with you to advance your HCV product portfolio in this rapidly developing market segment, for the benefit of patients worldwide.

Broad strategic access

QPS provides clients with broad access to its nonclinical and clinical development capabilities, as well as experience in nonclinical and clinical development of a diverse portfolio of treatment modalities for HCV. Our preferred vendor agreements also provide for the establishment of a client-dedicated unit within our organization.

Timely delivery

Partnering with QPS will position your company for success, enabling timely delivery of your HCV drug candidates to the marketplace.

Contact

Please contact us to help you navigate your way through the development of your HCV product portfolio:

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