Hepatitis C virus is a major public health issue and a leading cause of chronic liver disease. The current treatment—pegylated interferon and ribavirin—is associated with significant adverse events and sustained virologic response rates of only approximately 50% in genotype-1 patients. New drugs in development include novel interferons, ribavirin analogs, NS3 protease and NS5B polymerase inhibitors, and cyclophilin inhibitors. The primary goal of drug development is to improve efficacy; secondary goals include shortening the duration and increasing the tolerability of treatment. Viral resistance and toxicity must be overcome before acceptance of new drugs. Future therapy may likely be approved in the United States and European Union by 2011, including a combination of these novel agents, with interferon and ribavirin remaining key components.

HCV Virology
HCV is an enveloped virus belonging to the Flaviviridae family. The viral genome is a single-stranded RNA molecule with a 5′ untranslated region (UTR) containing an internal ribosome entry site for initiation of translation and a 3′ UTR responsible for RNA replication and packaging. The genome encodes for a polyprotein of approximately 3000 amino acids. The polyprotein is processed by host and viral proteases into four structural proteins (core, E1 and E2 envelope, and p7 ion channel) and six nonstructural proteins (NS2 cysteine protease; NS3 serine protease and helicase; NS4A serine protease cofactor; NS4B anchoring protein; NS5B RNA-binding protein; and NS5B RNA-dependent RNA polymerase) [7,8].

A basic review of the HCV life cycle allows a better understanding of potential targets of new drug development. First, the virus attaches to the hepatocyte and enters the cell through the low-density lipoprotein receptor. Neutralizing antibodies, vaccines, and receptor antagonists are potential therapies aimed at this step. Once the virus enters the cell, it is uncoated and the genome is released for translation and polyprotein processing. Thus, inhibitors of the internal ribosome entry site are a second potential therapeutic target. The virus then uses its own proteases and RNA-dependent RNA polymerase for replication and RNA synthesis. These are also prime targets for drug development. Finally, maturation of the virus requires subsequent steps in which inhibition of virus assembly and release could play a role (Fig. 1) [9].

Novel HCV Therapy
A partial list of experimental HCV drugs in advanced development is shown in Table 1.
Novel interferons

Albinterferon-α-2b (Albuferon; Human Genome Sciences, Rockville, MD/Novartis, Basel, Switzerland) is an 85.7-kDa molecule formed by the genetic fusion of human albumin and interferon-α. Combining interferon-α with albumin decreases clearance and prolongs drug half-life [10]. Phase 2 clinical trials suggest that albinterferon may be as safe and efficacious as pegylated interferon-α-2a but require fewer injections. These results were presented at the 58th annual meeting of the American Association for the Study of Liver Disease (AASLD) in 2007. Patients with CHC who were genotype 1 and treatment-naïve were placed in four treatment arms: pegylated interferon-α-2a, 180 μg weekly; albinterferon, 900 μg every 2 weeks; albinterferon, 1200 μg every 2 weeks; and albinterferon, 1200 μg every 4 weeks. All patients received weight-based ribavirin. SVR rates for these treatment arms were 58%, 58%, 55%, and 51%, respectively. The safety profile of albinterferon was comparable to pegylated interferon, and patient-reported missed work days were significantly fewer in the arm that received 900 μg every 2 weeks compared with the other arms [11]. Also presented at AASLD 2007 were the results of SVR rates after albinterferon treatment in previous treatment nonresponders [12]. There were five albinterferon treatment arms—1200 μg every 4 weeks; 900 μg every 2 weeks; 1200 μg every 2 weeks; 1500 μg every 2 weeks; and 1800 μg every 2 weeks—demonstrating an overall SVR of 10.7% in genotype-1 patients who were nonresponders to previous treatment with pegylated interferon and ribavirin [12]. In the phase 3 trials currently under way, treatment-naïve, genotype-1 patients were randomly allocated to receive ribavirin plus albinterferon, 900 μg every 2 weeks; albinterferon, 1200 μg every 2 weeks; or pegylated interferon-α-2a, 180 μg weekly for 48 weeks. Unfortunately, the 1200-μg dosage was associated with pulmonary adverse events, causing this arm to be dropped. A second phase 3 trial is evaluating genotype-2 or genotype-3 patients with similar arms to genotype-1 patients, but with a treatment duration of only 24 weeks. The results of these phase 3 trials are anticipated for 2009.

Omega interferon (Intarcia Therapeutics, Hayward, CA) is a novel interferon derived from Chinese hamster ovary cells. It shares 70% homology with interferon-α. The developers of this drug plan to have it ultimately delivered continuously via a subcutaneous implantable pump over 12 weeks [13]. The results of a phase 2 clinical trial were presented at the 42nd annual meeting of the European Association for the Study of the Liver (EASL) in 2007. Patients in this open-label trial with CHC, genotype 1 received omega interferon, 25 μg daily, alone or combined

**Figure 1.** Hepatitis C life cycle and targets of drug development. The virus must attach and enter the hepatocyte through a receptor. Upon entering the cell, the RNA is uncoated and released and the polyprotein is translated. The virus then uses its own protease and polymerase for replication and RNA synthesis. The virus is then matured, transported, and released from the hepatocyte.