HCV, initially uncovered more than 20 years ago[2] as the etiological agent responsible for non-A/non-B hepatitis, is a member of the (+)-RNA virus Flaviviridae (*Hepacivirus* genus) and occurs as seven major genotypes, which are comprised, in turn, of several subtypes and a multitude of quasi-species.[3] Genotypes 1a/1b are predominant, particularly in America, Europe and Japan. Until recently, the HCV standard of care (SOC) was limited to a combination of subcutaneously administered pegylated interferon-α (PegIFN) and an oral broad-spectrum antiviral, ribavirin (RBV). This treatment has suboptimal efficacy, particularly in the genotype 1 patient population (45–50%), and suffers from severe side effects and contraindications.[4] As scientists have gained understanding of the HCV life cycle, several attractive targets have emerged for alternative therapeutic intervention.[5] Protease inhibitors (PIs) rapidly took the lead as direct-acting antivirals (DAAs) and in 2011 two agents, Vitrelis from Merck and Incivek from Vertex, provided patients with improved treatment options, raising efficacy up to 75% (as measured by sustained virologic response, SVR) when administered in combination with PegIFN and RBV to treatment-naive patients.[6] Unfortunately, owing to its error-prone polymerase and the lack of a proof-reading mechanism, the use of single DAAs, even in combination with immunotherapy, results in the rapid emergence of resistant virus. Furthermore, these two drugs have not addressed tolerance issues, as specific drug-related side effects have merely reinforced those associated with the use of PegIFN/RBV. In the near future, more potent second-generation PIs (*e.g.*, faldaprevir and simeprevir) currently in Phase 3 clinical trials, in combination with PegIFN/RBV, may be expected to provide simplified dosing regimens and further improvement over current options.[7]

The virally encoded NS5B RNA-dependent RNA polymerase (RdRp) is a vital component of the replicase complex that orchestrates the replication process leading to the production of progeny virus.[8] The RdRp also attracted early interest from the research community and drug developers, since it does not have a mammalian counterpart and inhibition of this target is not expected to cause host toxicity. Furthermore, much precedent was available from HIV research to suggest that inhibition of polymerase activity offered an attractive opportunity for therapeutic intervention. Indeed, many classes of NS5B inhibitors (*e.g.*, nucleoside or nucleotide analogs, allosteric inhibitors) have progressed into clinical trials in recent years and have shown promising efficacy in chronically infected HCV patients.[9] However, in the case of non-nucleoside inhibitors (NNIs), the rapid emergence of resistant virus has hampered progress of these agents in monotherapy or in combination with SOC. Highly successful HIV HAART strategies, if applied to HCV, suggest, however, that a combination of DAAs targeting complementary and essential viral functions should provide a powerful approach to address the resistance issue. NS5B inhibitors are therefore expected to become an important component in the future of more effective and better tolerated anti-HCV regimens. Finally, a recent paradigm shift towards the development of interferon-free therapies using combinations of DAAs with complementary modes of action (*e.g.*, PI + NS5B or NS5A and also NS5B + NS5A combinations) is envisaged to provide