next 5 years. Of these, nucleoside polymerase inhibitors show strong pan-genotype activity with good potency and very high genetic barriers to resistance. As such, great optimism exists amongst medical professionals and drug companies alike that the burden of HCV disease will be dramatically reduced over coming years and that the gold standard of an effective, interferon-free, DAA combination regimen will be achieved.

However, a note of caution is pertinent, despite tremendous recent progress, and HCV may still take many years to be controlled effectively. Currently, single DAA efficacy, necessarily given with SOC, remains dependent on response to interferon and it will be several years before sufficient DAAs are available clinically to utilise combinations that lessen this dependence, although several interferon-free trials are ongoing. DAAs are also very expensive and will not be available in many developing countries where they may be needed most, plus patient compliance and identification remain a critical determinant of treating the considerable disease population. In addition, side effects and drug interactions[218] may be significant, with some severe reactions already documented for protease inhibitors.[219] Additionally, drug resistance remains a significant concern owing to the highly variable nature of HCV and its endemicity within populations likely to both rapidly mix and disseminate new strains, while failing to comply adequately with antiviral treatment, such as injecting drug users. Even highly potent nucleosides capable of initially clearing virus in combination with ribavirin for 8 out of 10 patients, in fact result in rebound several weeks later; however, additional combinations and/or interferon may prevent this in the long term. As such, even in the best-case scenario it is likely that HCV drug development may need to continue for many years and accommodate additional targets, much like the case of HIV-1. This will be especially important for those unable to tolerate existing treatments or infected with multi-drug-resistant virus strains that could emerge under such intense selective pressure. Finally, recent high-profile Phase 3 drug trials have been halted owing to severe adverse events, including patient deaths. Notably, the HCV nucleoside polymerase inhibitor BMS-986094 (formerly known as INX-189, developed by Inhibitex) has been discontinued following the identification of both cardiac and kidney toxicity which resulted in patient deaths. Trials of another nucleoside from Idenix Pharmaceuticals with similar chemistry are currently on hold, but studies are continuing for chemically distinct Gilead and Vertex lead drugs in this class. In addition, trials of Alisporivir (Novartis, formerly DEBIO-025 developed by the Swiss company Debiopharm[220,221]), which targets HCV–cyclophilin interactions, have been halted owing to a possible exacerbation of interferon-associated pancreatitis, again involving fatalities. The most up-to-date information on HCV drug trials can be found at www.natap.org.

9.2.3.2 Discovery of the HCV p7 Viroporin

HCV is the prototype for the *Hepacivirus* genus of the Flaviviridae, with a 9.6 kb positive sense ssRNA genome and forming an enveloped particle