virus carrying BIT225 resistance mutations may be present in non-responsive patients or in those where virus load may rebound at later stages of therapy. This will provide clinical clues as to its mode of action and also whether it may be useful against other virus genotypes. BIT225 and future p7 inhibitors may therefore become a useful addition to the HCV inhibitor repertoire, with applications both for the direct treatment of chronically infected patients and in a post-transplant and/or perinatal setting, where curtailing the amount of secreted infectious virus may be critical. Compounds with improved potency compared with prototypes, or even BIT225, may be derived from extended screening programmes or through solving p7 structures, plus the potential for combining separate classes of p7 inhibitor targeting peripheral/protomer/lumenal binding sites may yield significant clinical benefit by raising the genetic barrier to resistant HCV.

9.3 Other RNA Virus Viroporins: Prospective Targets for Emerging and Clinically Important Viruses

Many examples of (candidate) viroporins have been identified in RNA viruses where details pertaining to inhibitory molecules are lacking. Nevertheless, these essential virus proteins represent potential candidates for viroporin-focused therapy, especially in cases such as arboviruses where disease is self-limiting in humans, thereby minimising resistance concerns and where curtailment of symptoms is paramount for patient survival.

9.3.1 Viroporin Activities in Picornaviruses

Interest in developing picornavirus-targeted antivirals is considerable, particularly in the light of the programme intended for the eradication of poliovirus infection worldwide. The use of live vaccines has already been stopped in most countries, yet killed vaccines do not prevent gastrointestinal infection and virus shedding by chronic carriers, including some derived from live vaccines. Antiviral prophylaxis would represent an excellent means of curtailing outbreaks as the withdrawal of vaccines continues. Other clinically important picornaviruses such as enterovirus 71 (EV71), which causes widespread and severe disease epidemics in Southeast Asia,[262] generate an urgent need for vaccines and antiviral interventions. Lastly, the direct treatment of the common cold, primarily caused by rhinoviruses, would have huge socio-economic benefit.

Membrane permeability is markedly increased during the mid to late phase of picornavirus infection, culminating in cell lysis and release of infectious non-enveloped virions from the cell.[13] In particular, proteins encoded by enteroviruses (*e.g.* poliovirus, Coxsackie B virus, human rhinovirus) were shown to alter both bacterial and mammalian cell membrane permeability and also cellular membrane trafficking within infected cells.[12,13,66,69,70,263–268] Initially, the non-structural 2B, 2C and their precursor 2BC proteins were demonstrated