(http://www.clinicaltrials.gov/ct2/show/NCT00069511), although many of the patients involved were at advanced disease stages, making effective responses unlikely. Such studies understandably led to considerable scepticism concerning the worth of p7 inhibitors for HCV treatment; however, in retrospect in the light of the new era of HCV DAA, these trials were seemingly destined to fail according to the criteria by which they were measured. We now know, and probably should have guessed in the past, that the response to even potent HCV DAA (nucleosides perhaps being the exception), given singly with SOC, remains dependent on the interferon response.[261] Interferon-insensitive HCV therefore rapidly selects resistance to what essentially becomes DAA monotherapy. This would be expected to occur all the more rapidly for a DAA not targeting genome replication, such as an inhibitor of particle release. Furthermore, amantadine is known to be the least potent of the prototype p7 inhibitors identified to date,[64,243] which, combined with relatively low serum concentrations being achievable at standard doses (2–3 μM at best), likely results in a very low genetic barrier to resistance occurring, should the patient not already be infected with a naturally resistant strain. The potency of UT-231b was likely far higher than that of amantadine, yet again would face the rapid selection of resistance in interferon-insensitive HCV. In addition, the majority of patients in this trial had already failed SOC and were also clinically less likely to respond to therapy due to their disease state. Nevertheless, the selection of the Leu20Phe resistance polymorphism,[63,256] and possibly others,[257] in genotype 1b patients by an inhibitor as poor as amantadine is strong evidence that a selective pressure was exerted by the drug due to a specific antiviral effect, however weak it may have been. Therefore, potent compounds targeting p7 should be able to dramatically improve clinical outcome. Initially, effects will necessarily need to be measured in combination with SOC, yet ideally p7 inhibitors should be given alongside DAA targeting replication in order to minimise the potential for HCV to select resistant variants.

BIT225 represents the first bespoke p7 inhibitor to be tested in clinical trials and early reports presented at HepDART 2011 (http://www.natap.org/2011/hepDART/hepDART_22.htm) of its efficacy are encouraging: 87% of patients receiving 400 mg of BIT225 alongside SOC achieved an early virological response (12 weeks, $>3\log_{10}$ drop in virus load) compared with 61% for SOC alone. Furthermore, patients on 400 mg of BIT225 also showed an additional median $\log_{10}$ reduction in virus load after the 28 day dosing period compared with SOC alone. However, a greater proportion of the treatment group were infected with genotype 1a HCV, against which BIT225 was selected, compared with the control group (6/8 in the 400 mg group, only 2/8 in the controls), which may skew these data towards a favourable response in such a small cohort. Similarly, the small cohort size means that one or two patients may greatly affect the percentage median response rates; 5/8 SOC controls achieved an EVR, one less than the 6/7 in the 400 mg arm. Nevertheless, linear regression supported a statistically significant benefit ($p = 0.05$) and the treatment was well tolerated. It will be of great interest to determine whether