essential events required during efficient particle production. However, recent studies have shown that BIT225, which specifically blocks Vpu activity *in vitro*, does not interfere with Vpu-tetherin interactions[209] and others have shown that mutations blocking tetherin interactions have no effect on channel activity.[186] Therefore, Vpu, like other viroporins, demonstrates significant functional redundancy for such a small protein, possessing three seemingly distinct mechanisms of modulating HIV-1 particle production, although the role of channel activity *per se* is not clear. Interestingly, a recent study revisited the destructive interaction between the Vpu TM domain and cellular TASK channels, as reported previously by the same group. TASK channels help set the resting cell membrane potential and their disruption by both Vpu and/or a dominant negative TASK fragment serves to enhance HIV-1 particle release *via* enhancing depolarization-stimulated exocytosis.[210] Accordingly, HIV-1 release was accelerated by externally imposed depolarization alone, which reduced the barrier to membrane fusion/fission during budding. However, the relationship between this phenomenon and Vpu channel activity itself is not clear as the effects of Vpu inhibitors were not characterised.

Ambiguity surrounding the role of Vpu channel function should be resolvable *via* the use of inhibitors, yet specific resistance mutations to control for drug off-target effects have not been selected to date. Interestingly, *in silico* docking and molecular modelling predicted that HMA bound to a lumenal site in proximity to the functionally significant Ser24 residue,[211] yet unfortunately no biophysical or genetic evidence exists to support this. Similarly, no information as to how BIT225 interacts with Vpu channels has been published and no resistance mechanisms have been defined that may shed light on its mode of action. Nevertheless, BIT225 does not affect HIV-2, which lacks a Vpu protein, and it is reported to display activity against a wide range of both CCR5- ('R5') and CXCR4-tropic ('R4') strains.[86] However, whereas the compound appears potent against virus-infecting macrophages, its potency against T-cell-tropic cultured HIV-1 appears diminished, resulting in a far narrower selectivity index. This may reflect cell type-dependent effects whereby differential requirements for Vpu channel activity occur, consistent with the notion that BIT225 selectively targets macrophage resident virus reservoirs. Alternatively, it is possible that amino acid variation in the Vpu protein between R5 and X4 tropic strains might account for observed differences in potency, although how such strain variance may affect drug interactions has not been addressed *in vitro* or *in silico*. Such polymorphisms may point to sites of drug–protein interactions in lieu of cell culture-generated resistance mutants. Alternatively, output data from forthcoming BIT225 clinical trials may also provide resistance data for the drug in patients displaying viral rebound during treatment. Such trials represent a benchmark in the development of viroporin inhibitors as drug targets and their outcomes will be monitored with great anticipation. This may represent a stepping stone towards future Vpu inhibitors, selected from large-scale high-throughput screens or through the characterisation of protein–drug interactions and use of available TM domain structures in rational programmes.