~60 nm in diameter. A single open reading frame (ORF) is cap-independently translated from an internal ribosome entry site (IRES) yielding an ~3000 amino acid polyprotein, which is processed into the structural [core, envelope (E)1/2] and non-structural (NS) proteins by host and viral proteases. NS3/4A/4B/5A/5B forms the minimal viral replicase, as defined by sub-genomic replicon RNAs, whereas the NS2 protein acts as an autoprotease and also during virion production.

In 1994, a tenth HCV protein was discovered by groups analysing HCV polyprotein processing in the region between E2 and NS2.[222,223] A 63 amino acid protein, termed p7 according to its molecular mass, was produced following inefficient cleavage by signal peptidase at both the E2 C-terminus and, to a lesser extent, at the NS2 N-terminus; E2–p7 and E2–p7–NS2 precursors are therefore present within HCV-infected cells and over-expression studies have shown that cleavage at these sites is influenced by the preceding helical regions in E2 and NS2, respectively.[52,224] p7 was found to be highly hydrophobic and was predicted to contain two TMDs, separated by a short cytosolic (in accordance with polyprotein membrane topology) loop region containing two highly conserved basic residues.[225] Double membrane spanning topology was supported by cellular expression studies using epitope tags located at either termini and within the loop region, confirming p7 as a class 2 viroporin with its termini being lumenally oriented.[225] However, evidence that the C-terminal region of the protein may flip topology has also been demonstrated where p7 exists as an E2–p7 precursor,[52] and this has more recently been proposed to occur *in vitro* when p7 peptides are exposed to altered membrane compositions.[226]

In 2003, our laboratory demonstrated that recombinant p7 from HCV genotype 1b displayed channel activity in artificial bilayers with activity sensitive to low micromolar concentrations of amantadine.[37] Experiments were performed in a K^+ electrolyte and displayed both single-channel and burst-like activity. Activity was further enhanced by replacing K^+ with Ca^{2+}; however, it could not be ruled out that this was due to effects on membrane bilayers. p7 channel activity was subsequently confirmed later in the same year for synthetic peptides from genotype 1a HCV in K^+ electrolyte containing a low concentration of Ca^{2+}. Both single-channel and burst-like activity were again observed, with high conductance readings compared with recombinant protein.[38] In addition, nonylated but not butyl imino-sugars also effectively blocked channel activity when present at concentrations >100 μM. A year later, another synthetic genotype 1a peptide study also demonstrated p7 channel activity and highlighted 10-fold ion selectivity for K^+ and Na^+ over Cl^-, although this was lessened in the presence of even low levels of Ca^{2+}.[39] Conductance also adopted both single-channel and burst-like activity, with conductances similar to those in recombinant studies. This study also revealed that HMA at 100 μM also specifically inhibited p7 activity. Combined with the finding that p7 was essential for HCV to replicate in chimpanzees,[227] these studies sparked great interest in the development of p7 ion channel inhibitors as novel HCV therapies.