inhibitors have not been defined for SH channels, although the poor efficacy of available vaccines makes antivirals an attractive strategy to curtail acute respiratory illness, particularly in children.

9.3.4 Alphavirus 6K Proteins

The alphavirus genus of the Togaviridae are insect-borne arboviruses, usually transmitted by mosquitoes. They include significant human pathogens such as Chikungunya virus, Ross River virus and Venezuelan equine encephalitis virus, in addition to the genetic workhorses Sindbis and Semliki Forest viruses. Alphavirus structural proteins are expressed as a single polyprotein which is post-translationally cleaved by signal peptidase to generate the capsid, E1, E2 and 6K proteins; 6K is also acylated,[292,293] involved in both the trafficking and processing of the two major glycoproteins, and plays a major role in virion production as a minor virion component as well as trafficking functions; mutation and/or deletion of 6K results in the formation of aberrant virions with reduced thermal stability.[292,294–298]

Expression of 6K was first shown to induce bacterial hygromycin permeability, indicative of channel formation.[67] Topological predictions of its 61 amino acid sequence support its inclusion within class 2 viroporins, although *in vitro* studies supported a single TM topology.[16,17] These studies also demonstrated cation channel activity with preference for Na^+ and K^+ over Ca^{2+} and a 15-fold preference for Na^+ over Cl^-. The precise role of 6K channel activity has again been difficult to determine as mutations generally affect polyprotein processing, targeting, accumulation within virions or their budding.[294–296] Moreover, no small-molecule inhibitors have been described. Nevertheless, as limiting the disease course in Chikungunya and other alphavirus infections of humans can ameliorate long-term neurological damage occurring after encephalitis has passed, antiviral prophylaxis targeting 6K would be highly desirable.

9.3.5 Flavivirus M proteins

Flaviviruses comprise many significant human pathogens, including yellow fever virus, dengue virus, West Nile virus, Japanese encephalitis virus and tick-borne encephalitis virus. These arboviruses are primarily spread by mosquitoes or ticks and cause severe human disease, including encephalitis and haemorrhagic fevers. Much like alphaviruses, no antiviral therapies exist and patients are treated by symptom management. Ribavirin is sometimes administered in severe cases, although efficacy is limited.

Flavivirus M proteins are cleaved from the other envelope (E) protein by signal peptidase as a prM precursor,[299–301] then processed by resident proteases in the Golgi to generate mature M, a 75 amino acid protein which resides within the virion.[299,302] This cleavage event is essential to the production of mature flavivirus particles. Peptides corresponding to a proposed TM region in the C-terminus of dengue virus M protein displayed cation-selective channel