worldwide, these are controlled by vaccination and herd immunity. Of greater concern is the emergence of 'pandemic' influenza strains to which humans carry little or no immunity that can spread rapidly around the world. Such pandemics vary in severity, ranging from the 'Spanish flu' of 1918 (50 million deaths), to the 1957 pandemic (2 million deaths). Pathogenicity is impossible to predict prior to the emergence of pandemic strains. The recent H1N1 'swine flu' pandemic, although less pathogenic than the Spanish flu, spread rapidly owing to a lack of herd immunity and had both significant health and socio-economic impacts. H5N1 'avian flu' shows considerable pandemic potential and has infected hundreds of individuals with a >50% mortality rate, yet human-to-human transmission is currently rare. The possibility that avian flu could acquire the ability to spread efficiently from human to human is a global cause for concern, and recent controversial experiments demonstrated that only a limited number of genetic changes may be necessary for this to occur.[88,89]

As pandemics occur too rapidly for vaccination programmes to prevent worldwide spread of influenza, antivirals represent the best way to limit both the initial spread and the severity of virus infection for individual patients. Classically, influenza was treated using amantadine and rimantadine,[90] specific inhibitors of the viral M2 proton channel which plays vital roles during both virus assembly and cell entry. These drugs are now clinically redundant owing to viral resistance, occurring *via* defined point mutations in the M2 protein (*e.g.* S31N).[83] Current anti-influenza therapy focuses on a single target, neuraminidase, using the drugs oseltamivir[91–93] and zanamivir.[94–96] Recent detection of drug resistance for the more commonly used oseltamivir has raised concerns over the longevity of both compounds.[97] As M2 and neuraminidase inhibitors act synergistically in culture and suppress viral resistance,[98] new M2-targeted antivirals would be valuable additions to future combinatorial regimens.

9.2.1.1 *Identifying M2 as an Ion Channel Target of Amantadine*

Amantadine was approved by the US Food and Drug Administration (FDA) in 1966 for clinical use in the treatment of influenza virus infection under the trade-name Symmetrel. Amantadine was known to block an early stage of the influenza infectious cycle, but was also shown to affect later stages in a number of influenza strains.[1] Its methylated derivative, rimantadine (trade-name Flumadine), was later licensed (1994, FDA) in many countries as a more effective alternative with less pronounced side effects. It was not until 1985 that the molecular target of amantadine was identified through the selection of drug resistance in several amantadine-sensitive strains.[5] Mutations clustered within the *trans*-membrane region of the M2 protein, which is encoded on segment 7 of the influenza RNA genome and generated by alternative splicing.[99–101] In addition, the origin of the HA protein also impacted on amantadine sensitivity in strains where it affected the later stages of the life