A NEW CONCEPT IN ANTIVIRAL DRUG DESIGN

Lorena E Brown[1]

[1]Department of Microbiology and Immunology, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Victoria, Australia

Most antiviral drugs are designed to bind to and block the action of specific viral proteins. Here we introduce drugs designed to inhibit viral infection by creating an environment that is incompatible to replication. These drugs, which are the product of the Australian biotech company Aus Bio Ltd., are modular in structure, consisting of a viral attachment domain and an effector domain. We have initially tested the concept by creating drugs to counter influenza infection. Entry of influenza virus into cells is by receptor-mediated endocytosis. As the environment of the endosome becomes more acidic, the viral haemagglutinin (HA) undergoes a conformational change to reveal a hydrophobic fusion region that penetrates the endosomal membrane, a step necessary for the genome to escape the endosome and go to the nucleus for replication. The conformational change in HA is irreversible and if it occurs prior to contact with the cell, the virus is not capable of binding to the receptor and entering. The drugs use an attachment domain that binds to the neuraminidase glycoprotein and an effector domain that provides a negatively charged environment to trigger a premature conformational change in the neighbouring HA. These drugs have greatly enhanced *in vitro* potency compared to zanamivir and oseltamivir and unlike these neuraminidase inhibitors, the Aus Bio drug candidates show substantial inhibition of viral entry and of hemagglutination. Results with two of the lead candidates that show remarkable *in vivo* prophylactic and therapeutic effectiveness in the mouse model after a single dosing will be presented as well as preliminary data showing protection in the ferret model.