Wednesday April 13

Oral Session V
Immunomodulation and Drug Resistance

In Vivo Reconstruction Studies: Effects of pathogenic ACV-resistant virus on pattern of infection and clinical outcome. M.N. Ellis, E. Hill, R. Waters, D. Selleseth and D.W. Barry, Burroughs Wellcome Co., Research Triangle Park, NC, USA.

Defined mixtures of TK^+/TK^D or $TK^+/TK^D/TK^A$ HSV-1 viruses were used to infect athymic nude mice which received prophylactic (24 h before) or delayed (96 h PI) ACV in the drinking water. Mice inoculated with the $TK^+/TK^D/TK^A$ (76:17:7) mixture had a more rapidly progressing infection than mice receiving the TK^+/TK^D (70:30) mixture with lesion scores on day 4 of 2.3 vs. 0.6, respectively. Untreated mice infected with the $TK^+/TK^D/TK^A$ mixture were found to harbor ACV-resistant virus on day 6 while mice infected with the TK^+/TK^D mixture did not yield ACV-resistant virus until day 16. Mice receiving the TK^+/TK^D mixture responded poorly to delayed ACV treatment (0.5 mg/ml) while prophylactic therapy was quite effective in reducing lesion scores. Animals infected with $TK^+/TK^D/TK^A$ showed little clinical response to low doses of ACV (0.25 mg/ml) regardless of when treatment was begun. A 5-fold increase in ACV concentration (1.25 mg/ml) dramatically increased the effectiveness of prophylactic therapy while producing no change in response to delayed treatment. [^{125}I]-iododeoxycytidine (IdC) plaque autoradiography, as well as, in vitro ACV ED_{50}'s reveal a shift in virus population in favor of less sensitive virus during treatment. Yet, soon after termination of treatment TK^+ virus was again found in lesions. Our results indicate that small amounts of pathogenic ACV-resistant virus can influence both the pattern of infection, and clinical outcome.