I-40

New Inhibitors of Polyamine (PA) Biosynthesis and Their Effect on the Replication of Human Cytomegalovirus (HCMV). G. Arnett, L.M. Rose, E.L. White, W.B. Forrister, T.H. Moss III, R.W. Brockman, W.M. Shannon and J.A. Secrist III; Southern Research Institute, Birmingham, AL, USA.

HCMV infection of human diploid embryonic lung (MRC5) cells decreases the intracellular level of putrescine to 40% of control, increases spermidine (Sd) 3- to 4-fold, and increases spermine (Sp) 2- to 3-fold. The total PA pools are elevated about 2.5 fold. A series of analogs of the substrate for *S*-adenosyl methionine decarboxylase (AdoMetDC), an enzyme necessary for the synthesis of Sd and Sp, were synthesized and examined for their ability to inhibit AdoMetDC activity, PA biosynthesis, and HCMV replication. The series of inhibitors consists of compounds in which the methionine group of *S*-adenosylmethionine has been replaced by an N-methyl-N-[3-(hydrazino)propyl]amino group (MHZPA), an N-methyl-N-(2-aminooxyethyl) amino group (MAOEA), an N-methyl-N-[3-(hydrazinecarboxamido)propyl] amino group (MCHPA), or an N-methyl-N-[(2-hydrazinocarbonyl)ethyl] amino group (MHDEA). The concentration of compound in μM needed to inhibit AdoMetDC in a crude cell extract by 50% is: 0.005 for MHZPA, 0.07 for MAOEA, 0.22 for MHDEA, and 2.5 for MHCPA. At a concentration of 1000 μM, MHZPA lowered the yield of HCMV from 5.7 x 10^5 PFU/ml in control cells to 1.4x10^2 in treated cells. MHCPA at 320 μM produced a 2.5-$\log_{10}$ reductionin virus whereas MAOEA at 1000 μM produced only a 0.8-$\log_{10}$ reduction. In L1210 cells, these four inhibitors substantially reduced the PA pools, including that of Sp. In MRC5 cells, 320 μM MAOEA at 24 hours reduced the Sd pools by 13% and the Sp pools by 60%. (Supported in part by NIAID Contracts NO1-AI-42555 & NO1-AI-72642.)

I-41

Metabolism of BV-araU In HSV-Infected Cells
H. Machida[1], Y. Watanabe[1], T. Suzutani[2] and M. Azuma[2]
Res. Lab., Yamasa Shoyu Co., Ltd., Choshi, Chiba-ken[1] and Dep. Microbiology, Asahikawa Medical College, Asahikawa, Hokkaido[2], Japan

To study the mechanism of selective antiviral action of 1-β-D-arabinofuranosyl-*E*-5-(2-bromovinyl)uracil (BV-araU) on HSV-1, we examined the metabolism of BV-araU in the HSV-infected cells. [^{14}C]BV-araU was effectively taken up into HSV-infected human fibrobrast cells, but only a little amount of the labled compound was found in mock- or TK$^-$-HSV-1-infected cells. Most of [^{14}C]BV-araU was recovered from the acid-soluble fraction of cells. BV-araU was phosphorylated to its 5'-mono, -di and -triphosphates (BV-araUMP, BV-araUDP and BV-araUTP) only in HSV-1-infected cells. Main metabolite of BV-araU was BV-araUMP (about 89% and 96% of total radioactive compounds found in HSV-1- and HSV-2-infected cells, respectively), and a relatively small amount of BV-araUTP was observed. BV-araUDP was detected only in a limited amount in the infected cells. Thus, conversion of BV-araUMP to BV-araUDP may be the step limiting the phosphorylation of BV-araU to BV-araUTP. When dTMP synthesis was inhibited by 10 μM of FUdR, however, BV-araUMP disappeared resulting in an increase in formation of BV-araUDP (7%) and BV-araUTP (86%). Addition of thymidine caused markedly reversal of the activity of BV-araU and inhibition of further phosphorylation of BV-araUMP. These findings suggest that phosphorylation of BV-araU to BV-araUTP is essential for exhibition of its antiviral action and that phosphorylation of BV-araUMP to BV-araUTP competes strongly with that of dTMP to dTTP.