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Anti-Human Immunodeficiency Virus Activity of a Novel Synthetic Peptide, T22 ([Tyr^{5,12},Lys^{7}]polyphemusin II) — A Possible Inhibitor for Virus-Cell Fusion. **H. NAKASHIMA[1], M. MASUDA[2], T. MURAKAMI[1], Y. KOYANAGI[1], M. WAKI[3], A. MATSUMOTO[3], N. FUJII,[2] AND N. YAMAMOTO[1]** Department of Microbiology, Tokyo Medical and Dental University School of Medicine, Tokyo 113,[1] Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto 606,[2] and Seikagaku Corp., Tokyo 103, Japan[3]

The circulating hemolymph in invertebrate animals is known to contain many biologically active substances, such as antimicrobial peptides. They contribute to a self-defense system in the animal kingdom against invading microorganisms. We synthesized more than 40 peptides associated with tachyplesin and polyphemusin, which are highly abundant in hemocyte debris of the horseshoe crabs, Tachypleus tridentanus and Limulus polyphemus. Among these peptides, we found a novel compound which was called T22 ([Tyr^{5,12},Lys^{7}]polyphemusin II) strongly inhibited HIV-1 induced cytopathic effect and viral antigen expression being its 50% effective concentration 0.008 ug/ml while its 50% cytotoxic concentration was 54 ug/ml. The anti-HIV activity of T22 was observed with several strains of both HIV-1 including AZT-resistant strains and HIV-2 within the concentration range of 0.006-0.071 ug/ml. T22 efficiently inhibited giant cell formation in the cocultivation of MOLT-4/HIV and MOLT-4 cells, but it was not able to inhibit direct HIV-binding strongly. T22 did not inhibit RT activity, either. From the results of the time of addition study, which was monitored by the appearance of proviral DNA using PCR technique, T22 seems to exert its effect on the process immediately after virus adsorption, most probably virus-cell fusion.

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Clinical correlates of "In vitro" HIV-1 Resistance to Zidovudine. Results of the Multicentre Canadian AZT Trial (MCAT). **J. Singer, JSG Montaner, MT Schechter, J Ruedy, M. Fanning, C. Tsoukas, MV O'Shaughnessy, M Wainberg, Canadian HIV Trials Network, Vancouver, British Columbia, Canada.**

Objective: To describe the rate of development of "in vitro" HIV resistance to zidovudine (ZDV) and its prognostic implications within the multicentre Canadian AZT Trial (MCAT). **Methods:** HIV infected subjects at CDC groups IIB, III and IV-C2 with CD4>270/mm^3 were eligible to participate in the study. History, physical examination and laboratory evaluation were performed at regular intervals. Viral cultures were performed every 12 weeks in a subset of 50 subjects. An isolate was termed resistant (R) if it could be isolated from a 10 µmol ZDV containing medium. Kaplan-Meier (K-M) methods and Cox regression were used to describe time to resistance and its predictors. The relationship between the development of "in vitro" resistance and subsequent disease progression (to ARC, AIDS or death) was studies as follows: At each progression, 2x2 tables were constructed classifying progression vs resistance status. The observed progressions were compared with the number expected under the null hypothesis using Mantel-Haenszel methods stratified according to baseline CD4:CD8 ratio. **Results:** The K-M estimate for the cumulative development of "in vitro" resistance was 59% (95% CI: 37%, 73%) by 180 weeks. Baseline CD4:CD8 was negatively associated (p=0.08) with the subsequent development of resistance; proportional hazard=0.44 (95% CI: 0.17, 1.10). After adjusting for baseline CD4:CD8 ratio, the number of observed *vs* expected progressions following the development of resistance were 15 *vs* 7.27 respectively (p=0.008) as determined using the method of Mantel and Byar. Overall, progressions were more frequent in the lower CD4:CD8 ratio stratum; however, the observed vs expected progression still showed similar trends among subjects developing "in vitro" resistance when each CD4:CD8 was analyzed separately: These were 3 *vs* 1 and 9 *vs* 4 for the high and low CD4:CD8 ratio stratum respectively. **Conclusions:** "In vitro" resistance to ZDV developed in 59% of subjects after 33/4 years of ZDV therapy. Lower CD4:CD8 ratios at baseline were associated with faster development of "in vitro" resistance. In addition, the development of "in vitro" resistance was found to be a marker of subsequent disease progression to ARC, AIDS or death. This association remained even after adjusting for baseline CD4:CD8 ratio. Our data demonstrates that "in vitro" resistance to ZDV is associated with progression of disease among HIV infected individuals treated with ZDV. Whether "in vitro" resistance to ZDV is merely a surrogate marker or a determinant of disease progression remains to be established.