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Inhibition of HIV-1 Infection in Hu–PBL–SCID Reconstituted Mice by Rapamacyn

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Background: The capacity of the immunomodulatory drug Rapamacyn (RAPA) to inhibit replication of CCR5 strain of HIV in vitro prompted us to test its effects in a murine preclinical model of HIV infection.
Methods: CB.17 scid/scid mice, reconstituted by i.p. injections with 40×10^6 PBLs, were treated per os with 0.6 or 6 mg/kg bw of RAPA or its vehicle. Treatment was given daily starting two days before the i.p. challenge with the R5 tropic SF162 (1000 $TCID_{50}$/ml) and continued for three consecutive weeks.
Results: Within 3 weeks after infection, vehicle-treated controls exhibited a severe depletion of CD4 + T-lymphocytes (90%) an inversion of the CD4/CD8 ratio and the presence of HIV-DNA within peritoneal cells, spleens and lymph nodes. In contrast, RAPA-treated mice exhibited preserved CD4/CD8 ratio, decreased cellular provirus integration and reduction of HIV-RNA levels in the blood. In addition, in co-cultivation assays, spleens from RAPA-treated mice were uncapable of infecting allogeneic T cells. The effects of RAPA on these readouts were dose-dependent.
Conclusions: These data show that RAPA possesses powerful antiviral activity against R5 strains of HIV in vivo and warrant additional studies aimed at evaluating the potential use of this drug in the management of HIV patients.

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QSAR Analysis of Influence of Artifical Ribonucleases Structure on their Anti-influenza Activity

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"Chemical" ribonucleases hold promise as tools for studying the structures of RNAs and RNA–protein complexes, as reactive groups in conjugates intended for cleavage of particular RNAs, as therapeuticals inactivating virus genome RNAs or certain mRNAs, and as a promising antiviral agents. Drug design and development of new medicines directed against influenza virus are permanently actual tasks. The usage of modern QSAR (quantitative structure–activity relationship) methods could allow us to solve these problems more effectively. The objective of the present work is QSAR analysis of anti-influenza activity of various artifical ribonucleases. Inhibition of influenza virus A/Hong Kong/1/68 (H_3N_2) reproduction in tissue cultures of chorioallantoic membranes of chick embryos by studied compounds was tested. Anti-influenza activity is expressed in $lgTID_{50}$ (tissue infection dose) and reflected suppression of viral replication in "experimental" samples to "control". Hierarchic QSAR technology (HiT QSAR) based on Simplex representation of molecular structure has been used for the solution of the formulated problem. Consideration of different physical–chemical properties of atoms, the high adequacy and good interpretability of obtained models and clear ways for molecular design are the advantages of offered approach. Obtained QSAR models are quite satisfactory ($R^2 = 0.85$–0.9, $Q^2 = 0.7$–0.8). The influence of different molecular fragments on anti-influenza activity was defined. It has been discovered that the presence of methanol group, aminoacetaldehyde group and long aliphatic chain is an important factor promoting activity. Vice versa, the insertion of carboxyl into investigated compounds substantially decreases their anti-influenza activity. Virtual screening of anti-influenza activity of more than one hundred compounds taking into account the Domain Applicability of obtained models have been carried out. Some compounds have been selected for the experimental validation. This work was partially supported by PharmaMed RUXO-008-NO-06 grant.

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