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Glycoprotein 41 targeted radioimmunotherapy as a novel treatment for neuroHIV/AIDS

The HIV epidemic is a major global health threat. Nowadays HIV-infected individuals live much longer due to the inhibition of the viral replication by combined anti-retroviral therapy (cART). However, cART fails to eradicate the residual HIV-infected cells, therefore, virus persists and continues to cause damage both systemically and to central nervous system (CNS). HIV enters the CNS in infected monocytes shortly after peripheral exposure. The infection of CNS poses a challenge due to strict regulation of the entry of molecules into the brain by the blood brain barrier (BBB) which limits many cART regimens from reaching effective levels in the brain. Radioimmunotherapy (RIT) uses antigen-specific monoclonal antibodies (mAbs) for targeted delivery of cytocidal ionizing radiations to cells. The distinct advantages of RIT are its relative independence from the immune status of the patient and secondly, it is not subject to drug resistance mechanisms. These features are very useful in the management of HIV-infected individuals. The challenge in extending the RIT approach to the elimination of HIV in the CNS lies in the difficulty of the therapeutic molecules to penetrate through the BBB. Recently we have demonstrated that an antibody 2556 to gp41 was able to penetrate the in vitro human BBB and to kill infected cells in the brain compartment of the BBB model (McFarren et al AIDS 2016). In this study we have identified six human mAbs with higher pI (> 8.5) that recognizes a conserved region of HIV gp41. The penetration of these antibodies through in vitro human BBB model was pI dependent. We are now using these novel gp41-binding human mAbs conjugated with three different radioisotopes (213Bi, 188Re or 177Lu) enabling their more efficient penetration into the CNS through the intact BBB. To achieve this, monocytes are infected with HIV and then treated with radiolabelled mAbs. Finally, to validate these novel radiolabeled molecules, we will use a human in vitro BBB model to assess the ability of these mAbs to penetrate the BBB and to kill the HIV infected monocytes in the brain compartment of the BBB model. This study will provide a novel treatment option for the eradication of HIV-1 infection and will also be useful for treatment of drug-resistant HIV strains.

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Email Address

ravendra.garg@usask.ca

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Primary author: Mr GARG, Ravendra (University of Saskatchewan)

Co-authors: Dr EKATERINA, Dadachova (University of Saskatchewan); Ms MILLS, Kienna (University of Saskatchewan)

Presenter: Mr GARG, Ravendra (University of Saskatchewan)