Abstract of the Thesis

Synergistic inhibition of cell-to-cell HIV-1 infection by combinations of single chain variable fragments and fusion inhibitors

Background and Purpose: Cell-to-cell spread of HIV permits ongoing viral replication in the presence of antiretroviral therapy and is suggested to be a major contributor to sexual transmission by mucosal routes. Fusion inhibitors that prevent viral entry have been developed, but their clinical applications have been limited by weak antiviral activity, short half-life, and the low genetic barrier to development of resistance.

Methods: We examined the inhibitory activities of a series of single-chain variable fragments (scFvs) targeting the V3 and CD4i epitopes against both cell-free and cell-to-cell HIV infection.

Results: We found that all anti-V3 scFvs, including two newly constructed scFvs, showed broad neutralization activity against a panel of subtype B viruses compared with the corresponding IgGs. All scFvs neutralized cell-free infection by HIV-1JR-FL WT and fusion inhibitor-resistant mutants. In addition, all anti-V3 scFvs and some CD4i scFvs significantly inhibited cell fusion, while their IgG counterparts did not. Furthermore, combinations of scFvs and fusion inhibitors, such as C34 and SC34, showed synergistic inhibition of cell fusion by both HIV-1JR-FL WT and fusion inhibitor-resistant mutants. The most prominent combinational effect was observed for one of the CD4i scFvs, 916B2, with SC34. The delay in cell fusion in fusion inhibitor-resistant mutants partly explained the synergistic inhibition of resistant viruses by this combination.

Conclusions: Our data demonstrate the advantages of using scFvs over their parent IgGs for inhibiting both cell-free and cell-to-cell infection. Highly synergistic inhibition of cell fusion using combinations of scFvs and fusion inhibitors suggests the possibility of intensification therapy adding this combination to current anti-HIV treatment regimens.