GEORGE MASON UNIVERSITY
COLLEGE OF SCIENCE
DEPARTMENT OF BIOLOGY SEMINAR
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"Synergistic Inhibition of R5 HIV-1 by the Fusion Protein (FLSC) IgG1 Fc and CCR5 Antagonist Maraviroc in Primary Cells: Implications for Prevention and Treatment"

Antiretroviral (ARV) drugs targeting retroviral enzymes have been extensively employed to treat HIV-1 infection. Drawbacks of this approach include cost, toxicity, and the eventual emergence of resistant strains that threaten prophylactic and/or therapeutic efficacy. Accordingly, efforts to develop next-generation of ARV approaches are warranted, particularly if they can offer a higher threshold of resistance. We have previously shown that FLSC, a fusion protein containing gp120BAL and the D1and D2 domains of human CD4, specifically binds CCR5, an important cellular co-receptor, and inhibits the entry of R5 HIV isolates. (FLSC) IgG1, a fusion of FLSC and the hinge-CH2-CH3 region of human IgG1, has an increased antiviral activity, likely due to the resultant bivalency. In this study, we show CCR5 reduction upon (FLSC) IgG1 treatment both by standard flow cytometry and visualized techniques using a novel nanoparticle method. A β-lactamase virus-cell fusion assay was used to quantify (FLSC) IgG1 inhibition of HIV-1 entry into both cell lines and primary cells. Synergistic anti-viral activities of (FLSC) IgG1 and MVC in primary cells were evaluated by measuring supernatant p24 levels via ELISA and calculated using the MacSynergyTM II program.

We previously reported that treatment with the CCR5 small molecule antagonist Maraviroc (MVC) increased the apparent exposure of the (FLSC) IgG1 binding sites on CCR5, leading us to wonder if the two compounds used in combination might synergize in their anti-viral activity. Here we show that this is indeed the case. We demonstrate that fusion protein (FLSC) IgG1, strongly synergizes with the CCR5 antagonist Maraviroc to successfully inhibit both MVC-sensitive and MVC-resistant R5 HIV-1. Observed synergy between (FLSC) IgG1 and MVC was high in both, cell lines and primary PBMCs. This has relevance for future *in vivo* studies. In addition, synergy occurred both with MVC-sensitive viruses and MVC-resistant viruses, partially restoring the inhibitory effect of MVC. These findings suggest that a combinatorial treatment based on these two compounds has potential merit and that future *in vivo* studies are warranted.

TUESDAY December 6, 2016
3:00-4:15 PM
Innovation Hall Room 131