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Oral presentation

The Immunomodulatory Agent Rapamycin Potentiates the Antiviral Activity of the Fusion Inhibitor T20 Against R5 Strains of HIV-1

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The fusion inhibitor T20 marks the beginning of a new era in the management of HIV-1 disease. By inhibiting viral entry, T20 suppress viral replication in patients carrying strains resistant to reverse transcriptase or protease inhibitors. However, its antiviral activity is compromised by mutations in gp41. Based on our previous work demonstrating that Rapamycin (RAPA) inhibits R5 HIV-1 by downregulating CCR5 surface expression, we now show that RAPA and T20 synergize in antiviral activity against R5 strains. Synergy studies using the Median Effect analysis revealed that the IC50 values of RAPA and T20 in the RAPA/T20 combination were reduced 9- and 3- fold, respectively. Three-Dimensional modeling confirmed the observed synergy (synergy volume of 253.85; 95 % CL : 91–147). We also show that the RAPA/T20 combo, but not T20 alone, prevented the emergence of T20 resistance upon continuous passage of R5 HIV-1 ADA on PBMCs for 24 weeks under subinhibitory concentrations of T20. In addition, R5 ADA and YU-2 clones carrying T20 single mutations 36D, 38 M or 43 K (4–10 fold resistance) or the double mutation 36D/38 M (65-fold resistance), were all inhibited in the presence of RAPA. In conclusion, our results demonstrating that the RAPA/T20 combination has synergistic antiviral activity, prevents the emergence of T20 resistance, and inhibits T20 resistant strains, suggest a novel therapeutic approach to enhance the antiviral activity of T20 in patients carrying R5 strains of HIV-1.