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TMC120 BLOCKS HIV-1 INFECTION IN CELLULAR AND HUMAN CERVICAL TISSUE MODELS

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INTRODUCTION: TMC120 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that demonstrates potent anti HIV-1 activity, a good resistance profile and efficacy in the vaginal hu-SCID mouse model of transmission. To evaluate the potential of this drug as active ingredient in a microbicide formulation, we have investigated TMC120 as a base compound using cellular and human cervical explant models. Furthermore we have optimized its activity through rational formulation design.

METHODS: Anti HIV-1 activity of TMC120 (and formulations) was assessed by treatment of virus, cells, or human cervical explants with either base compound or formulated gel. In addition, activity in physiologically relevant fluid (semen and cervical mucus) has been established. The effect of TMC120 on the viability of vaginal epithelial cell lines and cervical tissue has been evaluated, with Nonoxynol-9 as a control. Furthermore, effects on cytokine expression have been measured by Bioluminex.

RESULTS: TMC120 inhibits HIV-1 infection by X4 and R5 strains of virus in both cell based assays and cervical explant models, including migratory cells emanating from human cervical explants. TMC120, alone and in formulation demonstrated excellent biocompatibility with cervical tissue and induced little or no modulation of cytokine production. Physiologically relevant fluids (semen and cervical mucus) had no effect on activity. Furthermore, TMC-120 demonstrated significant anti-HIV memory effects, with cervical tissue resisting viral challenge up to 6 days post treatment (2 hours) with TMC120. However, such memory effects were due to prolonged drug tissue levels rather than direct virucidal activity. Optimization of TMC120 formulation (0.005%) using

rational formulation design greatly increase activity of the compound providing a selective index of >1 in a billion.

CONCLUSIONS: TMC120 demonstrates good anti-viral activity in cellular and cervical explant models, and shows no toxicity at therapeutic levels. These data suggest TMC120 represents a promising candidate microbicide.

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