Strigolactones as antiviral drugs to inhibit Herpesvirus replication

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INTRODUCTION: The human cytomegalovirus (HCMV) is the most frequent cause of congenital malformations in developed countries. Although several nucleoside analogues have been employed successfully against HCMV infection, their use in children is hampered by the occurrence of serious side-effects, such as neutropenia and thrombocytopenia. Thus, there is an urgent and unmet clinical need for less-toxic, but highly effective, antiviral drugs that could be safely administered against HCMV during pregnancy or in the neonatal period. Strigolactones (SLs) are a novel class of plant hormones with multifaceted roles. While the activity of SLs in plant-related fields is well characterized, their effects on human cells and their application in medicine are still emerging. The main data reported so far refer to the effect of SLs on cancer cells. However, the antiviral activity of SLs has never been demonstrated so far. In the present study, a panel of SL derivatives, named TH-EGO, EDOT, EGO-10, and GR24, has been evaluated for their antiviral activity against Herpesvirus infections, focusing on HCMV.

MATERIAL AND METHODS: Viral yield, attachment, and entry assays were performed on Human Foreskin Fibroblasts (HFFs) treated with a non-toxic concentration of the selected compounds and infected with HCMV. Western blot, flow cytometry, and computational analyses were performed to identify the molecular mechanism beyond SL activity.

RESULTS: we demonstrated that TH-EGO and EDOT, and their derivatives TH-ABC and EDOT-ABC, markedly inhibit *in vitro* HCMV replication . We observed an inhibitory, but less pronounced antiviral effect also for other members of the Herpesvirus family, such as Herpes simplex virus type 1 and 2 (HSV-1 and HSV-2). Interestingly, SLs do not affect the first steps of HCMV replication (i.e. attachment and entry), but exert their role on the late phases, as indicated by a reduction of late protein expression, such as the HCMV tegument protein pUL99 (pp28). Finally, we pointed to the SL-dependendent induction of apoptosis of HCMV infected cells, during the late stages of infection, as a contributing mechanism to their antiviral properties.

DISCUSSION AND CONCLUSION: Overall, our results indicate that SLs could provide an alternative to nucleoside analogues in the treatment of herpetic infections.