ID der Kurzfassung : **112**

PD0184264, an active metabolite of the MEK-inhibitor CI-1040 shows superior pharmacokinetics and antiviral activity against influenza virus

Inhalt

Drugs directed against influenza virus directly show the tendency to induce resistance. We have previously shown that influenza virus (IV) highjack cellular factors for its own purpose and that the nuclear RNP export is strongly dependent on the virus-induced activation of the Raf/MEK/ERK signal pathway. Thus, this pathway is most favorable for antiviral intervention, because it is required by the virus to cross intracellular barriers, such as the nuclear membrane. We have shown that the MEK inhibitor CI-1040 demonstrated antiviral activity against IV in cell culture and in the mouse model. CI-1040 is a MEK Inhibitor that was originally developed by Pfizer for anti-tumor therapy. Here, we show that ATR-002 (PD0184264), the active metabolite of CI-1040, is more efficient in inhibiting IV propagation in vivo due to superior pharmacokinetics. We compare the kinase inhibitory potential of CI-1040 and ATR-002 in a cell free and cell dependent assay. Furthermore, antiviral activity of both compounds is demonstrated in vitro and after infection of mice with H1N1pdm09.
Treatment of mice with 25mg/Kg ATR-002 resulted in almost complete virus clearance in the lung. This effect could only be observed when 150mg/kg CI-1040 was used. Pharmacokinetic studies revealed that the ATR-002 appears to be clearly better absorbed in the antiviral mouse model compared to the mother compound. We now use ATR-002 as a candidate for further development in the direction to clinical investigations.

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