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P0487 The cellular kinase inhibitor AR-12 inhibits Zika virus in vitro and in vivo

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Background: Zika virus (ZIKV) is a human-pathogenic flavivirus that has recently emerged as a global public health threat. While most patients are asymptomatic or mildly symptomic, ZIKV infection may be associated with congenital malformations in infected fetuses and severe neurological and systemic complications in some infected adults. There are currently limited treatment options for ZIKV infection. AR-12 (OSU-03012) is a celecoxib derivative cellular kinase inhibitor with no inhibiting activity on cyclooxygenase that has antiviral activities against a broad spectrum of viruses, including dengue, Lassa, Ebola, and Marburg viruses.

Materials/methods: Clinical and laboratory virus stains representing the African and American lineages of ZIKV were included in the study. We evaluated the *in vitro* anti-ZIKV activity of AR-12, using cell protection and virus yield reduction assays, in multiple cell lines. We further evaluated the in vivo anti-ZIKV activities of AR-12 in the lethal type I interferon-receptor-deficient A129 mouse model. All experiments involving live animals were approved by the relevant ethics committee.

Results: AR-12 inhibited both African and American lineages of ZIKV in Vero cells. Moreover, AR-12 inhibited an epidemic clinical strain of ZIKV in multiple cell lines. The half maximal inhibitory concentration (IC50) of AR-12 against ZIKV is consistently <5 μM in multiple cell lines. ZIKV-infected A129 mice treated with intraperitoneally administered AR-12 had significantly better survival, lower clinical scores, and lower blood and tissue ZIKV RNA loads ($P<0.05$) than untreated control A129 mice. Histopathological examination revealed less inflammatory reactions and immunohistochemistry staining showed less abundant ZIKV-NS1 protein expression in the necropsied tissues of the AR-12-treated A129 mice.

Conclusions: AR-12 exhibits anti-ZIKV activity *in vitro* and *in vivo*. The treatment effects of AR-12 should be further evaluated in clinical trials involving ZIKV-infected patients with severe complications.