# Contribution Details

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## STAT2 is a determinant of yellow fever virus host tropism

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### Abstract

Yellow fever virus (YFV) is the etiologic agent of yellow fever. There are no antivirals available to treat yellow fever, and attempts to develop YFV-specific antivirals or to develop alternative vaccines have been hampered by the lack of an immunocompetent mouse model of yellow fever.

It has been reported that both the wild-type (Asibi) strain and the 17D strain of yellow fever infect mice with defects in type I IFN (IFN-I) signaling. This suggests that the IFN-I response serves as the major barrier to mouse infection. We have recently shown that YFV antagonizes IFN-I signaling in human and non-human primate cells and that the NS5 proteins of both YFV-Asibi and YFV-17D bind and sequester human STAT2 after interferon signaling. Furthermore, a YFV-17D mutant encoding an NS5 mutation that prevents interaction with STAT2 exhibits a replication defect in IFN-I-treated primate cells.

Here, we show that YFV NS5 is unable to bind murine STAT2 and inhibit murine IFN-I signaling. We map the region of human STAT2 to which YFV NS5 binds and show that it is the same region to which dengue virus (DENV) NS5 has previously been shown to bind. Interestingly, and in contrast to dengue virus, YFV NS5 is unable to bind human STAT2 in murine cells indicating that in addition to STAT2 there are other human-specific factors that are required for YFV NS5 to inhibit IFN-I signaling. We further show that hamster IFN signaling inhibits YFV replication and cannot be antagonized by the virus.