Role of Gas6, TAM receptors ligand, in the pathogenesis of Zika virus infection.


Abstract
Zika virus (ZIKV) represents a public health challenge to Brazil and the rest of the world, especially because ZIKV infection has been linked to neurological sequelae, such as congenital fetal syndrome. Here, we aim to verify the role of Gas6 in the pathogenesis of ZIKV infection, by evaluating the expression of Gas6 and TAM receptors in patients infected by the virus with different degrees of disease severity, and infection of different human cells in vitro.

Key words:
GAS6, Receptors TAM, ZIKA Virus.

Introduction
The Zika Virus (ZIKV) is an arbovirus of the genus Flavivirus, transmitted through the bite of the Aedes aegypti mosquito, and it became a public health problem1. In the Americas, there have been over 200,000 confirmed cases of Zika fever (ZF), 60% of those in Brazil alone1. Although the infection is generally asymptomatic, recent data show the link between ZIKV infection to neurological sequelae, such as congenital fetal syndrome, for instance1. Although it is far from clear all the mechanisms involved in the infection and how the ZIKV is able to cross barriers formed by endothelial cells (ECs), it has been shown that TAM receptors, especially Axl, act as a facilitator for the entry of the virus when it associates with the endogenous ligand Gas6 (Growth arrest-specific 6)2. In regard, this project aims to verify the role of Gas6 in the pathogenesis of ZIKV infection. First, we evaluated the expression of Gas6 and TAM receptors in ZIKV-infected patients with different degrees of disease severity and in different human cells infected in vitro. These data will provide a better understanding of the relationship between the Gas6/TAM receptor axis with the pathogenicity of ZIKV, which may have important therapeutic consequences.

Results and Discussion
Until now we observed an increase of the Gas 6 levels in the serum of patients infected by ZIKV (Figure 1). This increase is even higher in patients that had developed neurological complication, such as encephalitis or meningitis, compared with non-neurological patients, suggesting a link between Gas6 expression and disease severity. Furthermore, ZIKV infection of human monocytes (THP-1 cell line) in vitro upregulates Gas6 secretion in a time and viral load-dependent manner (Figure 2). This indicates that ZIKV stimulates the production of its own ligand, which could increase the efficiency to infect cells.

Conclusions
We demonstrated that Gas6 may have an important role in the severity of ZIKV infection, since its concentration is higher in neurological patients. However, it is not clear whether ZIKV infection itself can modulate the expression of its ligands, such as Gas6 and TAM receptors. Therefore, it is important to understand how these molecules are modulated and participate in the pathogenesis of the infection in humans.