Zika virus (ZIKV) is an emerging virus that has spread to many countries. Most ZIKV-infected patients are asymptomatic or experience mild symptoms. However, in pregnant women the virus passes the placenta and infects the fetus, causing severe birth complications, most notably fetal demise and microcephaly. ZIKV infection is also associated with an increased incidence of Guillain-Barré syndrome in adults. Our knowledge about innate immunity against ZIKV is very limited. This is at least partially due to the fact that the available methodologies to study ZIKV are restricted to only a few methods and do not allow site-directed mutagenesis of the viral genome. In the proposed project we will use a ZIKV BAC construct that results in the production of infectious ZIKV upon transfection into cells. The ZIKV BAC plasmid can be genetically modified allowing to introduce mutations or to insert new genes like GFP or luciferases. With this novel tool in hand, we plan to identify and characterize cellular restriction factors of ZIKV and analyze how the virus evades innate immunity. In parallel, we generate ZIKV reporters expressing luciferase or GFP and use them to screen peptide libraries derived from human body fluids and tissues to identify the most potent endogenous inhibitors of this novel human pathogenic virus. This work will lead to a better understanding of innate immunity against ZIKV and the development of novel peptide-based drugs against this novel human pathogenic and emerging pathogen.