Abstract

Zika virus (ZIKV) is an enveloped arbovirus from the *Flaviviridae* family that has been associated with over three-thousand cases of congenital syndrome as of April 2017. However, there remains an incomplete picture of its pathogenesis and no approved therapeutic is available for the prevention or treatment of ZIKV. In recent studies, we identified glycosaminoglycans (GAGs) as new surface receptors that may facilitate ZIKV's host cell invasion. Among the various GAGs, FDA approved anticoagulant heparin showed the strongest avidity to ZIKV envelope protein (ZIKV E) and has also been shown *in vitro* to successfully inhibit infection by other pathogenic flavivirus. Newly synthesized homogeneous heparin oligosaccharides retain commercial heparin's low immunogenicity, show excellent *in vivo* half-life, and without heparin's anticoagulant activity, should also exhibit enhanced safety even when administered during pregnancy. In a second recent study, we designed multivalent glycodendrimers having specific architectures that successfully inhibited against influenza viral infection *in vivo.* These synthetic dendrimers, however, are not biodegradable and spacing between ligands cannot be precisely controlled. Recently, we used our expertise in DNA origami to design structures that can form biocompatible 2D/3D nanoscale platforms arranging ligands into complex patterns with precise nanometer inter-ligand spacings, thus overcoming pitfalls of our dendrimer scaffolds. In ongoing experiments, we have begun to generate multivalent glycan arrangements templated by DNA origami 2D-sheet (ZIKV "wrapper") and 3D half circular structures (ZIKV "catcher") based on the spatial pattern and distance between putative GAG binding sites within ZIKV E (on ZIKV surface) and on the size of ZIKV particles. We propose to build on our discoveries of a GAG-binding receptor involved in ZIKV host cell entry, multivalent glycodendrimer treatment for influenza, and DNA origami to develop innovative, biocompatible therapeutics to prevent the vertical transmission of ZIKV. To advance this strategy, we propose two well-defined and focused specific aims:

1. Generate multivalent HPO-conjugates templated by two designer DNA origami nanostructures to optimize HPO-conjugate binding to ZIKV.
2. Validate the safety and efficacy of high affinity conjugates as ZIKV inhibitors using *in vitro* models.