ATTACHMENT OF THE SYPHILIS SPIROCHETE, TREPONEMA PALLIDUM, TO THE VASCULAR ENDOTHELIUM

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Introduction: Trepnemona pallidum is the causative agent of venereal syphilis, a human-specific sexually transmitted infection characterised by multi-stage disease and diverse clinical manifestations. T. pallidum undergoes rapid hematogenous dissemination, accessing distant organ sites and penetrating tissue, placental, and blood-brain barriers. Tp0751 is an adhesin that interacts with the host vasculature and mediates bacterial adherence to endothelial cells under shear flow conditions. This study explores Tp0751-mediated adhesion to the vascular endothelium.

Methods Tp0751, expressed in a non-infectious model spirochete [Borrelia burgdorferi (Bb-Tp0751)], was assessed for a gain-of-function adhesion phenotype using attachment assays. Interaction specificity was probed with competitive inhibition gain-of-function adhesion phenotype using attachment assays. Affinity chromatography coupled with mass spectrometry was used to identify endothelial receptors for Tp0751. Membrane receptors isolated from human umbilical vein endothelial cells (HUVECs) were incubated with Tp0751-affinity columns and interacting proteins were identified with mass spectrometry.

Results Here we demonstrate that Bb-Tp0751 adheres to HUVECs under stationary conditions. The laminin receptor (LamR) was identified as an endothelial receptor for Tp0751. LamR is a brain endothelial receptor for other neurotropic invasive pathogens, including Neisseria meningitidis. Current investigations will validate the Tp0751-LamR interaction and characterise the functional outcomes of Tp0751 adhesion to endothelial cells.

Conclusion These investigations reveal the mechanics of T. pallidum attachment to endothelial cells, the fundamental step in the process of T. pallidum vascular dissemination. A complete understanding of this process will provide opportunities to prevent T. pallidum attachment to the host vasculature to facilitate syphilis vaccine development.

IN VITRO ACTIVITY OF GEPOTIDACIN AND OTHER ANTIMICROBIALS AGAINST MYCOPLASMAS AND UREAPLASMAS

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Introduction Mycoplasma and Ureaplasma spp. are important pathogens of the respiratory and urogenital tracts. Antimicrobial resistance limits treatment options. Gepotidacin (GEP), a novel triazacacenaphthylene topoisomerase II inhibitor that inhibits DNA replication by a mechanism and target distinct from fluoroquinolones was tested against 85 isolates of Mycoplasma hominis (Mg), Mycoplasma genitalium (Mg), Ureaplasma parvum (Up), and Ureaplasma urealyticum (Uu) in comparison to azithromycin (AZI), clindamycin (CLI), tetracycline (TET), levofloxacin (LEV), and moxifloxacin (MOX). Organisms tested included strains known to be resistant to TET, LEV, and/or AZI. This work was supported by GSK and funded through OTA HHSO100201300011C with HHS/BARDA.

Methods MICs were determined using broth microdilution in accordance with Clinical and Laboratory Standards Institute Guidelines.

Results GEP was active against 25 Mg, MIC range 0.032–0.125 µg/ml, including 5 that were AZI-resistant, with MIC90 (0.125 µg/ml), equivalent to MOX. GEP was active against 10 Mg. MIC90 (0.032 µg/ml) was 4-fold < MOX. GEP MICs against 25 Mg ranged from 0.5 to 2 µg/ml with MIC90 = 2 µg/ml, making it less active than other agents, including MOX (MIC90 = 0.125 µg/ml), with exceptions of 1 LEV and 2 TET-resistant organisms, for which GEP MICs were unaffected. GEP was less active against 25 Ureaplasma spp. (MIC range 1–1 µg/ml), MIC90 = 0.8 µg/ml. There was no effect on GEP MICs in 9 Ureaplasma spp., with resistance to LEV, AZI, and/or TET. GEP minimum bactericidal concentrations for 4 isolates of Mg, 4 Hm, 4 Mp, 3 Uu, and 1 Up were >3 dilutions > MICs, indicating bacteriostatic effect.

Conclusion GEP warrants further study to treat infections due to Mycoplasma spp., particularly organisms resistant to other antimicrobials as it was active against isolates resistant to AZI, TET, LEV, and/or MOX.