DNA as microbicide to prevent *Neisseria gonorrhoeae* infections.

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Each year, *Neisseria gonorrhoeae* (Ngo) causes over 1.5 million new infections in the US, and >87 million worldwide. The appearance of multidrug resistant and extremely drug resistant Ngo strains and the limited number of antibiotics now available for treating Ngo infection have led the World Health Organization to classify the pathogen an urgent public health threat. New modalities for preventing Ngo infection are needed.

Recently, we reported that commensal *Neisseria* kill Ngo *in vitro* and in a mouse model of lower genital tract infection. Ngo is killed when it takes up commensal DNA, when the methylation signature of the incoming DNA is different from that in the pathogen, and when the DNA attempts to undergo homologous recombination with the pathogen chromosome. Indeed, any DNA meeting these criteria will kill Ngo. Ngo DNA does not kill commensal *Neisseria*, however. These and other results led us to propose that DNA can potentially be developed as a microbicide that acts specifically on Ngo (patent US10286016B2).

We designed 9 DNA molecules that contain sequences in Ngo but not commonly found in commensal *Neisseria*, sequences that encode DNA methyltransferases essential for Ngo viability, and other sequences that are essential for *Neisseria* viability. The molecules were tested for their ability to kill Ngo MS11 *in vitro.* All the constructs killed Ngo MS11 with different efficiencies, with constructs containing sequences from essential genes performing the best (~90% killing efficiency). The killing efficiency of the latter constructs was similar to that of Nel chromosomal DNA. One molecule, MB 14-1-15, was selected for further testing on a collection of Ngo isolates. MB 14-1-15, killed all low passage and antibiotic resistant strains tested at high efficiency (>90%) efficiency, and did not harm the tested commensal species (*Lactobacillus iners*, *Gardnerella vaginalis* and 3 commensal *Neisseria*). Finally, MB14-1-15 was incorporated into commercially available personal lubricants KY Jelly (KY) and Astroglide (AG), and the formulations examined for their ability to kill a collection of Ngo isolates. In all cases, MB14-1-15 killed with an efficiency similar to that of the positive control (MB14-1-15 in Tris). Our results illustrate the potential of using DNA molecules containing Ngo chromosomal sequences as a microbicide for preventing gonorrhea infections during sexual intercourse.