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INHIBITION OF E. COLI HEMOLYSIN DURING URINARY TRACT INFECTIONS

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Value Proposition: *Potential adjunctive therapy for E. coli pyelonephritis to mitigate the renal tissue damage associated with infection, thereby reducing renal scarring and other long-term complications of renal scarring.*

Technology Description

Researchers at Washington University in St. Louis have engineered Fc fusion proteins with low-density lipoprotein receptor (LDLR) family members that can be used to block the activity of a toxin secreted by uropathogenic *E. coli* (UPEC) during pyelonephritis. The alpha-hemolysin (HlyA) of *E. coli* has been recognized for some time, but its mechanisms of action have been elusive, owing largely to its instability and difficulty with typical protein purification and structure determination. Our work has identified a new receptor for HlyA on epithelial cells (namely LDLR) and showed that LDLR is required for toxin internalization into epithelial cells and ultimately cell death.

This technology would act as an adjunctive treatment for inpatients with pyelonephritis in addition to IV antibiotic therapy. In the future, such treatments might also be useful in other severe *E. coli* infections such as sepsis. As the toxin is not carried by all pathogenic *E. coli*, molecular diagnostics could rapidly identify patients that might benefit from toxin-directed therapies.

Stage of Research

Have now shown in mouse models of *E. coli* pyelonephritis that HlyA causes damage to renal tissue, with no direct effect on colonization (i.e., bacterial loads in the kidney). Have identified for the first time that the cytotoxicity of HlyA to renal epithelial cells requires clathrin-mediated endocytosis and the expression of low-density lipoprotein receptor (LDLR).

Publications

Hunter W. Kuhn, Madeleine R. Smither, Rachel J. Jin, Christina A. Collins, Hongming Ma, Jason Sina, Joseph P. Gaut, Michael S. Diamond, David A. Hunstad. LDL receptor-mediated endocytosis of *Escherichia coli* α-hemolysin mediates renal epithelial toxicity.

Commun Biol 2026; https://www.nature.com/articles/s42003-026-09946-8.

Applications

- Treatment of UPEC infections

Key Advantages

- Adjunctive therapy for pyelonephritis that may mitigate long-term sequelae
- Future application to other severe *E. coli* infections

- Complementary to existing treatments and independent of antibiotic resistance patterns

Patents
Patent application filed

Related Web Links – David Hunstad Profile**;** Hunstad Lab