TITLE: Molecular genetic analysis of kidney stone prevention by the bacterium *Oxalobacter formigenes*

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RESEARCH PROJECT DESCRIPTION

Oxalobacter formigenes is a normal gut flora bacterium that is associated with decreased incidence of kidney stones. The bacteria consume dietary oxalate, the major component of most kidney stones, but more important, stimulate the intestinal epithelium to excrete oxalate from the blood. This lowers blood and urinary oxalate and therefore kidney stones. The mechanism by which *O. formigenes* stimulates oxalate excretion is unknown, but must involve either secreted or surface components of the bacteria.

Our goal is to identify the mechanism by which *O. formigenes* stimulates oxalate excretion so that improved probiotics and/or therapeutics can be developed. We will use molecular genetic manipulation of the bacterial genome in conjunction with animal models.

In this project, we will use transposon mutagenesis to identify knockouts of genes encoding surface or secreted products and a bioinformatic approach to guide knockout of individual genes most likely to encode the oxalate excretion stimulating factor. Mutants from both pools will be used to colonize mice fed an oxalate-rich diet, and we will measure oxalate in urine collected in metabolic cages to determine if the mutant *O. formigenes* fail to decrease urinary oxalate. Such mutants will be subjected to additional genetic analysis to identify the affected gene, confirm its role in oxalate excretion, and biochemical and physiological analysis to determine its molecular function.

Eventually, the oxalate excretion-stimulating factor will be purified and administered to mice or the gene(s) cloned into probiotic bacteria for treatment of mice to lower elevated oxalate levels.