OBJECTIVES: Huntington's disease (HD) is a progressive and fatal neurological disorder caused by an expanded CAG repeat in the gene coding for a protein of unknown function that has been named huntingtin. The exact cause of neuronal death in HD is unknown, however, recent findings in transgenic animals, cell models, and in humans have suggested that N-terminus proteolysis products which can form aggregates in the cytoplasm or nucleus may be toxic. Because tissue transglutaminase cross-links proteins into filamentous aggregates and polypeptide-bound glutamines, it has been hypothesized that transglutaminase may possibly underlie aggregate formation in HD. We have recent evidence that transglutaminase activity is increased in HD and in HD animal models. Our novel preliminary data, using the transglutaminase inhibitor, cystamine, as a therapeutic treatment, significantly improves the behavioral and neuropathologic phenotype and extends survival in the R6/2 transgene murine model of HD.

RESEARCH DESIGN: In the proposed two-year experiments, we will administer cystamine, as a therapeutic compound, in the R6/2 and N171-92Q transgene murine models of HD to determine whether we can ameliorate the degenerative changes observed and subsequently increase survival, as well as improve the clinical symptoms observed in these mice.

METHOD: These studies will be designed to extend and confirm our preliminary data, to provide critical information on i.p. and oral dosing, and to determine the efficacy of cystamine-in both pre and post-natal applications.

FINDINGS: Cystamine treatment significantly extends survival in the N171-82Q model of HD by 17.9%. In addition, cystamine treatment significantly improved motor performance; delayed loss of body weight, gross brain weight and atrophy, and striatal neuron atrophy; and greatly attenuated the development of mutant-htt aggregates. Levels of Tgase activity and Tgase 2 immunoreactivity were greater in N171-82Q mice than in littermate control mice and were reduced by cystamine treatment. Tgase immunoreactivity colocalized to mutant htt aggregates. Cystamine treatment significantly increased free GGEL, a specific biomarker for Tgase, in the N171-82Q mice, consistent with a therapeutic effect. Proteinbound GGEL immunoreactivity determined histologically was markedly increased in N171-82Q mice and colocalized with mutant htt aggregates. These findings demonstrate that cystamine has significant efficacy in improving the behavioral and neuropathologic phenotype observed in the N171-82Q transgenic model of HD and suggests that Tgase may play a role in HD. These findings confirm those previously reported in the R6/2 HD model. Our findings underscore the importance of the power of transgenic mouse models of HD for the screening of novel therapeutics. The positive effects of cystamine in N17182Q transgenic mice provide further evidence that Tgase may contribute to HD pathogenesis, although it is unclear what role other mechanisms of action of cystamine may play in improving both the behavioral and neuropathological phenotype.

CLINICAL RELAVENCE: These studies may not only help elucidate the role transglutaminases play in aggregate formation and whether inhibition affects the toxicity of mutant huntingtin, but most importantly provide a novel therapeutic strategy which may translate to human clinical trials and subsequent treatment of HD. In the next year, we will compare cystaine analogs.