

EX VIVO GENE THERAPY FOR THE PRESERVATION OF RETINAL AND
CENTRAL NERVOUS SYSTEM STRUCTURE AND FUNCTION IN A CANINE
MODEL OF CLN2 NEURONAL CEROID LIPOFUSCINOSIS

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Abstract

CLN2 neuronal ceroid lipofuscinosis is a recessively inherited lysosomal storage disease characterized by progressive motor and cognitive decline, seizures, vision loss progressing to blindness, brain and retinal atrophy, and childhood death. CLN2 disease results from mutations in the *TPP1* gene that encodes the soluble lysosomal enzyme tripeptidyl peptidase-1 (TPP1). We conducted studies using a canine model of CLN2 to determine whether continuous delivery of TPP1 protein to the retina and central nervous system could delay the onset and slow progression of retinal and neuronal degeneration. Autologously derived mesenchymal stem cells (MSCs) from CLN2-affected Dachshunds were transduced with an adeno-associated virus (AAV2) packaged DNA construct that directs stable overexpression and secretion of TPP1. The transduced cells were implanted into the ocular vitreous within the eye or the brain at an early stage of disease. Retinal structure and function as well as neurological function and cerebral atrophy were then monitored over time. TPP1-MSC treated eyes exhibited preservation of retinal-mediated responses to light stimuli and delayed progression of disease-related retinal. CNS treated dogs did not display an adverse reaction to the treatment and studies are currently ongoing to evaluate the extent of their potential neuroprotective effect.