Lay summary

The safety and efficacy of presymptomatic**,** intrathecal administration of 2-hydroxypropyl-beta-cyclodextrin (HPßCD) was evaluated in the feline model of Niemann Pick type C (NPC) disease and published in February 2015[1]. These studies would not have been possible without NNPDF support. Direct administration of HPßCD into the spinal fluid of presymptomatic cats with NPC disease prevented the onset of tremors and ataxia, and resulted in survival of Purkinje cells and a reduction in the storage of brain cholesterol and sphingolipids. However, an increase in hearing threshold was identified as an adverse effect[1].

Funding from the NNPDF was obtained in order to expand our breeding colony to allow for the production of additional affected cats. These cats are being used to develop methods to optimally treat NPC cats after signs of NPC disease have begun (postsymptomatically), and to develop methods to decrease hearing loss. Initial studies showed that post-symptomatic therapy prolonged lifespan and slowed the progression of neurological disease. However, no cat in this group survived beyond one year of age, and reduction is cholesterol and ganglioside storage in the brain was less profound than in cats treated presymptomatically. These data suggest that presymptomatic therapy is most effective at slowing disease progression and that cholesterol and ganglioside storage may be more difficult to correct post-symptomatically. The additional cats are being used to evaluate the effect of dose, frequency of administration, and age at administration on outcome.

Studies in both the mouse and cat have shown that HPßCD causes extensive damage and death to hair cells of the inner ear. Potential methods to decrease HPßCD-mediated hearing loss include 1) limiting access or concentration of HPßCD to the inner ear, 2) adjunct therapy with otoprotective agents, 3) using other cyclodextrins which may be less ototoxic, or 4) managing hearing loss with either hearing aids or cochlear implants. Thus far, we have attempted to limit the concentration of HPßCD to the inner ear by administering it into the CSF farther from the ear (lumbar cistern versus cerebellomedullary cistern). We found that administration of HPßCD at the lumbar cistern resulted in brain concentrations less than that found following cerebellomedullary cistern injection. Although hearing loss was decreased, efficacy was similarly decreased supporting our hypothesis that the dose measured at the cerebellomedullary cistern may correspond with both efficacy and ototoxicity.

1. Vite, C.H., *et al.* Intracisternal cyclodextrin prevents cerebellar dysfunction and Purkinje cell death in feline Niemann-Pick type C1 disease. *Sci Transl Med* **7**, 276ra226 (2015).