

**September 30, 2013**  
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**NNPDF Research Grant ~ Final Report**  
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**Lay summary of research performed for “The Fellowship of the Cats”.** Funding from the NNPDF allowed us to increase our breeding colony size of NPC1 cats in order to produce up to 30 affected cats per year for experimental therapy studies. These studies included evaluating the following drugs for the treatment of NPC1 disease: 1) intrathecal administration of 2-hydroxy-propylbetacyclodextrin (HP $\beta$ CD) to treat central nervous system (CNS) disease, 2) intrathecal administration of HP $\beta$ CD and subcutaneous administration of HP $\beta$ CD to treat both CNS and liver disease, and, 3) intrathecal administration of HP $\beta$ CD and oral administration of miglustat to treat CNS disease. These studies were successful in identifying the dose of HP $\beta$ CD that effectively treats disease in the CNS and liver and limits drug-associated hearing loss in the cat model. Although some treated cat are now over 2 years of age (untreated cats die at 6 months of age), they are showing some signs of NPC1 disease. We are now focused on characterizing what is happening in these older, treated cats, and on devising methods to prevent these abnormalities from developing. These studies were also successful in providing spinal fluid and blood to Dr. Ory’s lab in order to evaluate the effect of therapy on disease biomarkers, and to evaluate the accuracy of these biomarkers.

The studies in the cat are critical for guiding the clinical trials proposed in children as they help determine both safe and effective drug doses, as well as provide information on the best way to monitor treated patients. Finally, maintenance of the breeding colony allows us to rapidly begin evaluating safety and efficacy of any new potential therapeutic drugs after they demonstrate efficacy in cell culture.