NNPDF-Funded Research Grant # 32

TITLE: Therapeutic Gene Delivery to the Cerebellum in Niemann-Pick Type C
PROJECT INVESTIGATOR: Timothy M. Cox, MD, FRCP, FMedSci & Robin Henry Lachmann, M.A., M.B., Bchir, Ph.D.

PERIOD: 7/1/2003 - 8/31/2004

PROJECT DESCRIPTION

Niemann-Pick Disease Type C (NP-C) is a fatally progressive neurodegenerative disorder caused by an inherited defect in lipid trafficking. No specific treatment is currently available. Theoretically, gene therapy could provide a definitive cure for this devastating condition. This approach would require delivery of a therapeutic gene to large numbers of neurons throughout the brain and, at present, this is not a realistic goal. With the currently available vectors it is, however, possible to deliver potentially therapeutic genes to smaller, anatomically defined populations of neurons. The neuropathological hallmarks of NP-C are lipid storage, morphological changes and neuronal loss. The pattern of these changes has been well characterised in the BALB/c npcnih mouse, a murine model of NP-C. In these animals the Purkinje cells of the cerebellum are affected by lipid storage and show the characteristic morphological changes associated with glycolipid storage diseases. In addition, Purkinje cells are subject to a remarkable patterned degeneration which occurs in a stereotyped manner as the disease progresses. The aim of this project is to use a herpes simplex virus-based vector to deliver the potentially therapeutic transgenes NPC1, Rab7 and Rab9 to a defined subset of Purkinje cells in the anterior lobe vermis of the cerebelllum of the BALB/c npcnih mouse. We will determine the efficacy of these transgenes in reversing lipid storage, normalising neuronal morphology and preventing degeneration at the level of the individual neuron. If successful, these experiments will provide a proof of principle for the use of gene therapy in this condition.

FINAL STATUS REPORT
Dated 8/31/2004

The aim of this project was to investigate the possibility of gene therapy in the NP-C mouse. We have made a genetically engineered virus which will deliver a functioning NPC1 gene to neurones. We wanted to investigate if we could use this virus to deliver NPC1 to the cerebellum, a part of the brain which is particularly affected in NP-C. We performed experiments where the virus was injected directly into the brains of mice: several weeks later, we took the brains and tried to detect NPC1 in the neurones within the cerebellum.

Unfortunately, although we can deliver other proteins, to date, we have not been able to deliver NPC1 to significant numbers of neurones in the mouse brain. It is possible that different vectors, which are being developed in our laboratory and elsewhere will be more efficient. At present, gene therapy for

NP-C is still a long way off and small molecule therapies, which we are also actively investigating, seem more promising.

PUBLICATIONS:

No Publications on this Work To Date