Summary: September 1st 2010 – September 1st 2013

In vitro modeling of Niemann-Pick type C (NPC) disease using patient-specific induced pluripotent stem cells

In Niemann-Pick type C (NPC) disease a fatal neurodegeneration that is often accompanied by the dysfunction of liver and spleen leads to death of the patients. The most prominent biochemical feature of NPC1-deficient cells is an excessive storage of cholesterol and other lipids in the late endosomal/ lysosomal (LE/ L) compartment of cells. The sequestration of cholesterol in neurons (i.e. astrocytes, microglia, Purkinje cells) impairs the myelination of axons and leads to dysfunction and death of the cells. The therapeutic options for treatment of NPC disease are very limited. There is an urgent need to improve existing therapies and develop new treatments.

Embryonic stem (ES) cells are pluripotent cells derived from the inner cell mass of mammalian blastocysts. ES cells not only have the capacity to self-renew but also can differentiate in to virtually all cell types of the adult body, e.g. cells of the neuronal lineage and the liver. The potential use of human ES cells (hESCs) for regenerative medicine has therefore gained high interest over the past years. Recent advances in the *in vitro* generation of human induced pluripotent stem cells (hiPSCs) from human fibroblasts opens up a new promising source for regenerative medicine. hiPSCs share common features with hESCs and can be used to generate many different mature cell types. hiPSCs may provide a great opportunity to develop new treatment strategies for patients that suffer from neurodegenerative diseases such as Niemann-Pick type C (NPC), Parkinson's and Alzheimer's.

The main goal of the presented research project was to use hiPSC technology to generate *in vitro* models of NPC diseases by differentiating of NPC patient-specific iPSCs (hNPC1 iPSCs) into various cell types of brain and liver. These patient-specific cells will allow us for the first time (I) to investigate the effect of different mutations in the disease processes and (II) to develop new treatment strategies.

We were able generation and characterization factor-free hNPC1 iPSCs from different patient and adequate control fibroblast lines. We further differentiated generated NPC1 iPSCs into cells of the brain and liver. Analyzing the cholesterol metabolism generated cell types we confirmed that these cells establish disease related phenotypes. The goal of using iPSC derived human brain and liver cells is to get a better understanding of NPC function and thereby develop new therapeutic strategies.