Summary: March 2011 – September 2011

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 by ectopic expression of four transcription factors, Oct4, Sox2, Klf4 and/or c-Myc, opens up a new promising source for regenerative medicine. Human induced pluripotent stem cells (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 is to use hiPSC technology to generate *in vitro* models of NPC diseases by differentiating of NPC patient-specific iPS cells (hNPC1 iPSCs) into various cell types of brain and liver. The generation of hNPC1 iPSCs will allow us to use human disease affected cell types to discover novel therapeutic compounds and develop new treatment strategies.

In the last months my work was mainly focusing on the generation of tools to derive and analyze disease affected cell types. I generated hNPC1 iPSCs from various patient fibroblasts lines carrying different mutations by introducing the four reprogramming factors Oct4, Klf4, Sox2 and c-Myc. Subsequently the reprogramming factors were excised from the genome of derived iPSCs to generate so called "factor free" hNPC1 iPSCs.

After successful generation of hNPC iPSCs our goal was to differentiate them into cells of the neuronal and hepatic lineage. Therefore I set-up differentiation protocols based on work done in our and other laboratories and differentiated generated hNPC1 iPSCs into different cell types of both lineages.

In the next month I will focus on the characterization of NPC affected cell types. These patient-specific cells will allow us for the first time to study disease processes and the effect of different compounds used for treatment of patients *in vitro* in NPC affected human cells such as neurons and hepatocytes.