Dr. Dorothea Maetzel - "In Vitro modeling of Niemann-Pick type C Disease Using Patient-Specific Induced Pluripotent Stem Cells"

"Dr. Maetzel's project will lead to development of pluripotent stem cells from human NPC mutant fibroblasts. The stem cells will then be used for high throughput assays to identify small molecules that can correct the cholesterol accumulation in the NPC cells. Development of these cell lines will allow testing of whether the genetic defect can be corrected in the stem cells, which could have therapeutic potential."

Dr. Dan Ory, Chairman, Scientific Advisory Board, NNPDF

Lay Summary

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

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Niemann-Pick type C (NPC) disease is a rare genetic disease (~1/150,000 live births) predominantly caused by a variety of single nucleotide mutations in the NPC1 gene (95% of the cases) 1. The mutations are inherited in an autosomal recessive manner and lead to loss of NPC1 protein function. In the majority of cases patients are affected at an early age. A fatal neurodegeneration that is often accompanied by the dysfunction of liver and spleen 1-3 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. It is caused by a defect in cholesterol export 1. 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. In very severe cases of the disease patients die due to liver failure often without developing neurological symptoms, since the liver has a central role in liver and lipid metabolism2,4. Previous studies in NPC-/- mice show that lipid metabolism is regulated by distinct mechanisms but regulatory elements have not yet been identified. The therapeutic options for treatment of NPC disease are very limited and 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 5. The potential use of human ES cells (hESCs) for regenerative medicine has therefore gained high interest over the past years 6. 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 7. Importantly, this process does not involve nuclear transplantation and the use of eggs and hence can be applied to many different patient cell samples. hiPSCs share common features with hESCs and can be used to generate many different mature cell types. Transplantation of functional tissues derived from hiPSCs may provide a great opportunity to treat patients that suffer from neurodegenerative diseases such as Niemann-Pick type C (NPC),

Parkinson's and Alzheimer's. Proof-of-principle models for the therapeutic use of hiPSC-derived neurons and blood cells in mice have already been established 8.

In this proposal I will use the hiPS cell technology to generate *in vitro* models of NPC diseases by differentiating of patient-specific iPS cells (hNPC1 iPSCs) into various cell types of brain and liver. These patient-specific cells of the neuronal and hepatic lineages will allow us for the first time to study disease processes *in vitro* in NPC affected human cell neurons and hepatocytes. More importantly the potential to generate high numbers of neuronal and hepatic cells will allow us to use these cells for chemical screens to discover novel therapeutic compounds.

Given that hiPSCs can be genetically manipulated by gene targeting, I plan to correct NPC1 mutations in selected hNPC1 iPSCs. The phenotypes of neurons and hepatocytes generated from corrected cells will be compared to those of diseased and healthy cells. These approaches will establish if gene therapy or cell replacement therapy based approaches can revert the diseased-phenotype of neurons and hepatocytes in NPC patients. This can open new lines of treatments with broad clinical implications.