Hematopoietic stem cell-directed gene therapy for Ataxia Telangiectasia

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Hematopoietic stem cell-directed gene therapy can be applied to cure monogenetic disorders of the blood system. In this approach, autologous hematopoietic stem cells (HSCs) are taken from the patient, modified ex vivo (by either introducing a healthy coding sequence of the mutated gene by for example retroviral vectors or by gene editing methods) and then transplanted back into the patient.

Since Ataxia Telangiectasia (A-T) is a monogenetic, autosomal recessive disorder caused by mutations in the ataxia telangiectasia mutated (ATM) gene, a gene therapy approach would be a choice for A-T patients to improve disease outcome. Because the encoded Atm protein kinase plays a major role in DNA damage response, the absence of the Atm protein or functionality leads to a multi-organ manifestation. Progressive cerebellar degeneration, telangiectasia, immunodeficiency (impaired B- and T-cell development, which leads to recurrent sinopulmonary infections), radiation sensitivity and a predisposition to cancer are the most prominent clinical signs. The recurrent infections can cause lung damage and in the end also lung failure, which is together with the development of tumors the main cause of death in A-T patients. The 20-year survival rate of A-T patients is around 50.0%.

We aim to develop HSC-directed gene therapy for A-T using lentiviral gene transfer. The Atm knockout mouse mirrors the human disease phenotype well and can be used as preclinical model. Due to the large size of the ATM coding sequence, we follow several approaches to optimize gene transfer into ATM-deficient HSC.