Safety of genome editing as therapy for autosomal dominant osteopetrosis

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Autosomal dominant osteopetrosis (ADO) is one of the most frequent hereditary skeletal disorders and characterized by recurrent fractures, bone pain, and additional complications. ADO is secondary to impaired activity of the bone-resorbing cells, the osteoclasts, which are derived from circulating blood cells, the monocytes. This osteoclast impairment is caused by dominant negative mutations in the gene CLCN7 encoding the chloride/proton exchanger ClC-7. No causative therapy exists for ADO and the current therapeutic concepts used for other, lethal forms of osteopetrosis cannot be applied due to an unfavorable benefit-risk profile. We therefore aim at developing a therapeutic strategy using genome editing. In a proof-of-concept study, our approach resulted in a restoration of ADO-osteoclast resorptive activity in vitro. In this project, the safety of this therapeutic approach will be investigated. The main risk of therapeutic genome editing is off-target editing at genomic sites that may induce oncogenic transformation leading to hematologic malignancies. A genome-wide monitoring of off-target editing will be performed using the DISCOVER-seq strategy. After optimization of the method for use in cells of the hematopoietic lineage chromatin immunoprecipitation using MRE11 antibodies will enrich DNA fragments flanking double strand breaks induced by therapeutic genome editing. By next-generation sequencing of these DNA fragments and bioinformatic analysis the localization and frequencies of off-target editing will be identified. In a subsequent candidate approach these aberrant editing sites will be independently validated. The results are an important step towards a clinical application of this ADO gene therapy.