With several clinical approvals, the field of oligonucleotide therapeutics has come of age in the last years. Simultaneously, the discovery of the CRISPR-Cas system has revolutionized manipulation of genetic information in cells and organisms. However, therapeutic application of DNA editing with CRISPR suffers from the unresolved safety issues due to unpredictable potential off-target effects.

More recently, several approaches have evolved to escape the risk of permanent DNA damage by targeting RNA instead. Yet, all approaches for site-directed RNA editing require the ectopic expression of a protein in addition to the expression or application of an RNA molecule and suffer from partially severe off-target RNA editing. In this thesis, it was sought to combine the advantages of site-directed RNA editing with the advances of oligonucleotide therapeutics. Therefore, antisense oligonucleotides to harness the endogenous RNA editing enzyme ADAR for site-directed RNA editing were designed, an approach we refer to as RESTORE (recruiting endogenous ADAR to specific transcripts for oligonucleotide-mediated RNA editing).

Various chemical modifications resulted in precise and efficient editing with a superior off-target editing profile compared to all other existing RNA editing approaches. The applicability of RESTORE could be demonstrated in a wide panel of human cell lines and with even better editing yields of up to 80% in human primary cells.

Furthermore, pathogenic mutations found in severe genetic disorders as Rett syndrome, alpha-1-antitrypsin deficiency and Hurler syndrome could be edited. To demonstrate the therapeutic potential of RESTORE, the IDUA W402X mutation was edited in primary fibroblasts donated from two Hurler syndrome patients. Importantly, the wild-type phenotype could be partially restored and an enzyme activity of up to 6-fold higher than that of the much milder Scheie syndrome could be reached.

Finally, to transfer this promising approach to *in vivo* applications, the antisense oligonucleotides were further improved with chemical modifications, enhancing stability in serum and cerebrospinal fluid. Moreover, this made unassisted gymnotic uptake of the antisense oligonucleotides into primary cells possible. Together with the successful recruitment of murine ADARs, this paves the way to *in vivo* applications and the development of RESTORE as a new class of oligonucleotide therapeutics.