Chemically Enhanced Antisense Oligonucleotides: A Molecular Approach for Treating Autosomal Dominant Tubulointerstitial Kidney

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Uromodulin, a predominant urinary protein, is produced by epithelial cells of the thick ascending limb (TAL) in the renal nephrons[1,2]. Mutations in the *Umod* gene, responsible for uromodulin production, can lead to autosomal dominant tubulointerstitial kidney disease (ADTKD) – a prevalent hereditary cause of progressive chronic kidney disease with limited treatment options[3–5]. To tackle this problem, we constructed a chemically enhanced antisense oligonucleotide (ASO) library to inhibit the translation of *Umod* mRNA and prevent its toxic accumulation. The design of our gapmer ASOs focused on two targets: the wild type (wt) sequence and a single nucleotide polymorphism (SNP) associated with severe ADTKD. The wt-targeting library is formulated to decrease overall uromodulin levels, providing a broad-spectrum approach to treat known ADTKD-UMOD cases. On the other hand, the SNP-targeting library aims to serve as a precision molecular tool to study SNP-discrimination and allele-selective oligonucleotide therapies, although with a narrower therapeutic scope. We identified a lead ASO that selectively silences an adverse disease-causing SNP (R185S) in vitro. Additionally, in vivo investigations into the ASO's silencing potency and bio-distribution were conducted post-subcutaneous administration in mice. Results show a promising uptake into the TAL cells and moderate silencing of *Umod* mRNA. This study demonstrates the potential for Umod as a molecular target of therapy and the TAL cells as a site of accumulation for this class of drugs.

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