# Repurposing COVID Vaccine mRNA Technology for Therapy of Cystinosis

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**Purpose:** Oral cysteamine therapy for cystinosis was developed forty years ago. The drug achieves partial clearance of cystine from lysosomes and delays organ deterioration -- but does not avert the eventual need for kidney transplantation or the eventual deterioration of other organs. Conceivably, this is caused by the poor tolerability of cysteamine. However, recent evidence suggests that Cystinosin protein has multiple jobs in the cell -- some of which are beyond the reach of cysteamine. We hypothesize that the mRNA/LNP technology used for the COVID vaccine can be repurposed to repair all functions of Cystinosin protein.

**Methods:** In collaboration with Moderna, we designed mRNAs for both the major (*CTNS*$^{LYS}$) and minor (*CTNS*$^{LKG}$) isoforms of CTNS, with "tags" that allow us to track the resulting proteins. To validate the Moderna CTNS mRNAs, we introduced them into proximal tubular cells from controls and patients. We then asked Moderna to package CTNS mRNAs into a novel "lipid nanoparticle" (LNP) similar to that in COVID vaccine. These were injected into healthy mice to see whether this would express normal Cystinosin in organs relevant to cystinosis.

**Results:** High levels of exogenous Cystinosin were detected in normal proximal tubular cells (using biochemical methods). By immunofluorescent microscopy, we visualized Cystinosin in lysosomes and other appropriate compartments within the cell. We then confirmed that this Cystinosin was fully functional. Within 24 hours, it completely normalized cell cystine cystine levels. Furthermore, it rescued another abnormality typical of cystinosis, the abnormal accumulation of autophagosomes in the cell.

24 hours after injection of LNP containing CTNS mRNA into healthy mice, we detected robust levels of Cystinosin in tissues such as kidney, lung, pancreas, heart, liver and bone marrow, On the other hand, we did not detect Cystinosin expression in skeletal muscle or brain.

**Conclusions**: Moderna mRNAs for the two CTNS isoforms produce high levels of functional Cystinosin in cultured cells. A novel Moderna LNP delivers CTNS mRNA and expresses Cystinosin protein in a variety of organs relevant to cystinosis. Future studies will determine where within each organ, the Cystinosin is found in healthy and Ctns mutant mice with cystinosis.
These pre-clinical studies should be valuable as a first step toward future clinical trials.