An mRNA/Lipid-Nanoparticle Strategy to Treat Cystinosis.

Paul Goodyer, MD and Elena Torban, PhD
Research Institute of McGill University Health Institute
Montreal, QC, Canada

If cystinosis patients are treated with oral cysteamine within the first 3 years of life, cystine accumulation is decreased and organ deterioration is slowed by 5-10 years. However, up to 1/3 of patients do not appear to benefit from treatment as much as others, most will eventually need kidney transplantation and it is unknown whether cysteamine prevents late deterioration of neuromuscular tissues. A therapeutic advance beyond what can be achieved with cysteamine is clearly needed.

With the advent of the COVID pandemic, Moderna, Pfizer and other companies used a new mRNA technology to express COVID protein fragments in our tissues; this induced our immune system to make protective antibodies. In collaboration with Moderna, we propose to adapt the mRNA platform to express specially stabilized *CTNS* mRNA in cystinotic cells isolated from our patients and then test the Moderna *CTNS* mRNA/lipid nanoparticle delivery platform in mutant *CTNS* mice.

mRNAs for the two main forms of cystinosin were designed with molecular tags that could be tracked in various ways. The first round of 10 such mRNAs have been produced by Moderna and preliminary experiments are under way to optimize uptake and expression of *CTNS* mRNA in kidney tubular cells isolated from patient urine. We will next screen the mRNAs most impact on abnormalities typical of cystinotic cells. Once the best reagents have been identified, Moderna will package them in lipid nanoparticles to test for targeted delivery to key tissues affected in cystinosis. We will study uptake and expression in mouse normal mouse tissues and then measure the impact on features of cystinosis after injection into *Ctns* mutant mice.

These pre-clinical studies are designed to lay the groundwork for an eventual clinical trial of this exciting new technology in the treatment of cystinosis.