Targeting autoimmune kidney disease with lipid nanoparticles

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Chronic kidney disease (CKD) affects millions of people worldwide, with ANCA-GN being one of the most severe and rapidly progressing forms. ANCA-GN leads to inflammation and destruction of kidney tissue, often resulting in end-stage kidney disease that requires dialysis or transplantation. Current treatments using immunosuppressants are only partially effective and come with severe side effects. Given the limited therapeutic options available, there is a critical need for innovative approaches for treating ANCA-GN.

Our goal is to restore the balance of harmful effector T-cells (Teff) and protective regulartory T-cells (Tregs) in the kidney. This can be achieved by either locally delivered immunomodulatory agent or intracellular delivered FoxP3 mRNA. A major challenge in kidney therapy has been delivering therapeutic agents effectively to the kidneys. For this, novel lipid nanoparticle (LNP) system that accumulates in inflamed kidney has been developed, providing a targeted and efficient delivery vehicle for bioactive agents or mRNA. The results demonstrated high kidney accumulation of these LNPs in animal models of ANCA-GN (Figure 1).

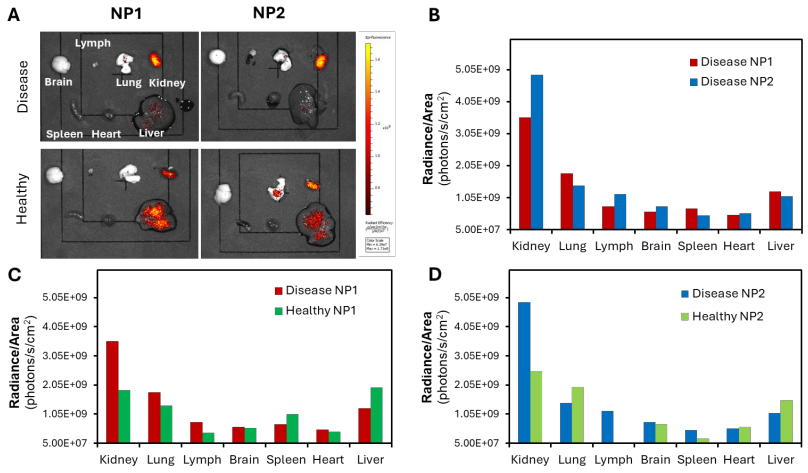

Figure 1. *In vivo* biodistribution of novel LNP formulations, NP1 and NP2, in mice. Cy5.5-tagged LNPs were administered to ANCA-GA disease or healthy mice via IV injection. Organs were harvested and imaged at 72 hr. Image analysis showed that both NP1 and NP2 accumulate in inflamed kidneys at a much higher level compared to any other organs (including the liver) (B). In healthy mice, the LNPs were also found in the kidneys but at a lower level compared to in inflamed kidneys (C and D). This data highlights the ability to accumulate preferentially in inflamed kidneys of our novel LNP formulations.

Using these LNP, all trans-retinonic acid (ATRA) or Foxp3 mRNA were encapsulated. Figure 2 showed improvements in animals treated with ATRA-NP. Histology results showed that there was less kidney damage found in mice treated with ATRA-NP. Furthermore, the albumin:creatinine ratio was much lower in ATRA-NP treated mice, indicating better function of the kidneys. Interestingly, we found much higher number of Tregs in the kidney after ATRA-NP treatment, suggesting their role in the improved clinical parameters. The number of Tregs in the spleen, however, remained the same.

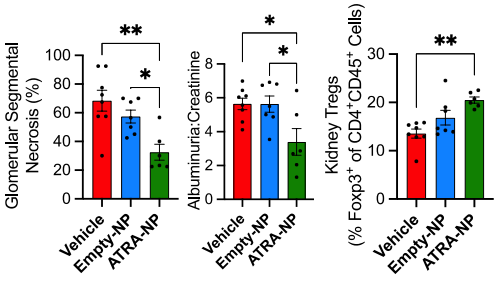

Figure 2. Clinical findings showed less kidney damanges and improved kidney functions in animals treated with ATRA-NP. Elevated Tregs were found in the kidney.

Preliminary data showed that the LNP encapsulates mRNA at high efficiency while maintaining kidney tropism in disease model. This provides an opportunity to reprogram T-cells in situ, which has not been achieved before.