ABSTRACT # 27

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Title: Systemic in utero gene editing as a treatment for cystic fibrosis  
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Background: Treating cystic fibrosis (CF) patients early is crucial in preventing or delaying irreversible organ damage. We hypothesize that early intervention through in utero gene editing could correct disease causing mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene during the initial stages of pathogenesis, potentially allowing for normal organ development, disease improvement, and possibly cure. We previously showed that gene editing to correct the F508del mutation can be achieved efficiently and safely in adult animals via intranasal administration of biodegradable nanoparticles (NPs) loaded with peptide nucleic acids (PNAs) and donor DNA. Further, we established that NPs can be safely administered to fetal mice, using intravenous (IV) or intra-amniotic (IA) delivery. This study aims to demonstrate that PNA/DNA NPs can correct the F508del mutation in utero, resulting in sustained postnatal CFTR function.

Methods: We determine if in utero treatment with PNA/DNA NPs targeting the CFTR locus can be used to correct the F508del mutation and lead to sustained postnatal functional CFTR activity in multiple disease-affected tissues in a mouse model of CF.

Results: We found that in utero PNA/DNA NP delivery to fetal mice resulted in significant mutation correction and functional CFTR activity after both IA and IV NP treatment. Systemic treatment resulted in sustained chloride flux, at a level similar to that of wild-type mice, in nasal and gut tissue. Additionally, bronchoalveolar lavage fluid analysis indicated a decreased inflammatory response in the lung of treated mice, compared to untreated CF mice.

Conclusion: A single in utero treatment of PNA/DNA NPs can effectively correct the F508del mutation before birth, resulting in sustained postnatal functional disease improvement.

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