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Gene corrected stem cell therapy to treat cystic fibrosis development at Stanford University

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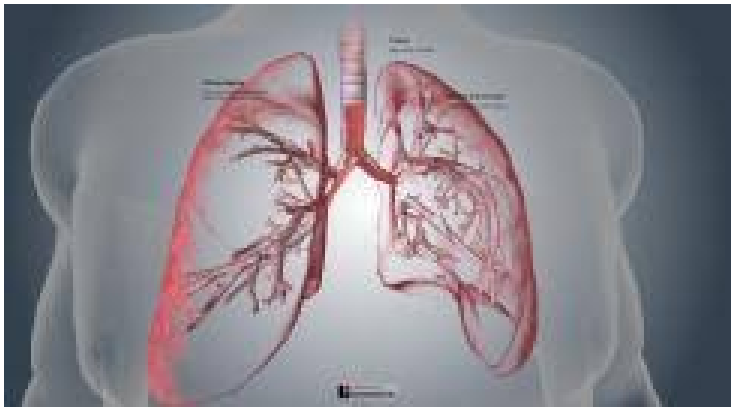
Cystic fibrosis affects about 75,000-100,000 people globally



A team of researchers at Stanford University has used the gene editing tool commonly known as CRISPR to repair the gene that causes cystic fibrosis in airway stem cells, which they say is a critical step to develop a gene therapy for the disorder.

The researchers showed that the repaired airway stem cells could give rise to other airway cells and could produce functional cystic fibrosis transmembrane conductance regulator protein, which is faulty in cystic fibrosis patients. The study represents a proof of concept for the repair of genes that cause airway disorders. A study describing these results was published online in *Cell Stem Cell* on December 12, 2019. Postdoctoral scholar Sriram Vaidyanathan, PhD is the first co-lead author and Matthew Porteus, MD, PhD, professor of pediatrics is the lead co-senior author. Other co-lead authors include Ameen Salahudeen, MD, PhD, Zachary Sellers, MD, PhD, Dawn Bravo PhD. Other co-senior authors include Tushar Desai, MD, Jayakar Nayak, MD, PhD and Calvin Kuo MD,PhD.

A devastating childhood disease: Cystic fibrosis affects about 75,000-100,000 people globally. CF patients suffer from chronic lung infections that eventually cause lung failure and death. In addition, patients may also suffer from problems in several other organs. CF patients have an average life expectancy of about 40 years. CF is a fatal disease caused by mutations in a single gene (the cystic fibrosis transmembrane conductance regulator (CFTR)). The CFTR gene encodes an ion channel that transports chloride in cells that express the gene. In CF patients, the channel is non-functional and chloride transport is blocked. This results in a build-up of thick mucus in the airways and also results in damage to other organs such as the pancreas.

The quest for a cure: Gene therapy has been attempted to treat several genetic diseases such as sickle cell disease and thalassemia over the past two decades with some individual successes. The discovery of CRISPR enabled the precise manipulation of genes and made it feasible to develop gene therapies for many more diseases. CRISPR was most readily applied to develop cures for blood disorders such as sickle cell disease because of our increased familiarity with blood stem cells and our ability to readily culture and transplant them into patients. Indeed, the first clinical trials to test the use of CRISPR to treat sickle cell disease, a blood disorder, have already started even though the technology is relatively new.

Although CF was one of the first diseases for which gene therapy was attempted, attempts have been unsuccessful so far.

The development of CRISPR renewed hopes for a gene therapy for CF. The application of CRISPR to treat lung disorders such as CF was challenging because methods to apply CRISPR to effectively edit airway stem cells had not been developed. The team consisting of Dr. Vaidyanathan, Dr. Porteus and colleagues have developed a method to correct one CF causing mutation (DF508) which affects over 70% of patients in the US and Europe. This publication describes the correction of a commonly observed CF causing mutation with efficiencies over >40% in airway stem cells. This is over a 100-fold improvement over previous work correcting the same mutations in other cell types and makes it possible to correct CF causing mutations in a clinically applicable manner. Further work is necessary to perfect the transplantation of edited airway stem cells in the airways to develop a durable treatment for CF.

Not just a disease that affects Caucasians: In addition to Dr. Vaidyanathan, another co-first author and two of the co-corresponding authors leading this work are people of Indian origin. However, CF is not widely recognized as a disease that affects Indians. CF has been described in Indian patients previously.[2,3] However, the exact number of CF patients in India is still unknown and the mutations that affect them are also not well characterized. It is likely that India has the largest number of CF patients in the world. It is also likely that most of them are undiagnosed and die before the age of 5. One study quantified the presence of CF in people of Indian origin in Canada and estimated the prevalence to be 1 in 9200 compared to 1 in 6600 among the general population between the ages of 0-14 years.[4] In fact, Dr. Vaidyanathan has come across patients at Stanford University who received a diagnosis for CF after significant delay. In some cases, CF was even deemed unlikely because the patients were not of European origin. This is rather unfortunate because the quality of life and life expectancy of CF patients can be significantly improved if treatment is started early in life. This new gene therapy approach thus holds the promise to treat CF patients globally once a method to transplant airway stem cells is optimized.