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Gene Therapy for Cystic Fibrosis: **Advancing the Promise of Future Treatment**

Highlights:

- Cystic Fibrosis (CF) treatments have advanced dramatically over the past 10 years
- There is no approved gene therapy for CF, but many are in development and show promise for future treatment
- Sponsors planning a CF gene therapy study should work to develop a patient-centric protocol and emphasize patient education and awareness

The Unmet Need

Cystic Fibrosis (CF) is a rare, genetic disease that can lead to lung infections, respiratory failure, and damage to the liver and pancreas. According to the Cystic Fibrosis Patient Registry, more than 30,000 people in the United States and 70,000 worldwide live with the disease. In the 1950s, a child diagnosed with CF rarely lived to see elementary school. Today, people with CF live well into adulthood.

While advances in pharmaceutical and nonpharmaceutical treatments are helping people with CF live longer, higher quality lives, more work remains. Gene therapy may provide lasting lung function improvement and, at best, a cure.

Sponsors planning a CF gene therapy clinical trial pay utmost attention to the needs and expectations of the CF patient population. While more than 75% of people with CF are diagnosed by age two, over half are age 18 and older.

CF Gene Therapy History

Researchers from the University of Michigan in Ann Arbor and the Hospital for Sick Children in Toronto, Ontario, discovered the CFTR gene responsible for CF in 1989. Proof-of-concept studies for CF gene therapy followed soon after.

Results from the first gene therapy clinical trial were published in 1993. While those early studies were not successful, they set the scene for researchers who made significant progress in the space over the next two decades.

CTFR Modulators Advance Treatment

Over the past 10 years, four FDA-approved therapies that target mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene have become available. These therapies are the first treatments to address the cause of the disease — a malfunctioning protein made by the CFTR gene.

These therapies have been shown to improve lung function in people with CF. However, they only work on specific mutations, and there are more than 1,700 known mutations in the CFTR gene that can cause CF.

While the CFTR modulators represent a landmark advancement in CF treatment, there are no approved CF therapies that provide a correct copy of the CFTR gene. Gene therapy could, in theory, work for anyone with CF regardless of mutation, but it cannot repair existing organ damage.

Even so, researchers around the globe are pursuing CF gene therapies, studying adeno-associated viruses (AAVs), lentiviruses, messenger RNA (mRNA), and transfer RNA (tRNA) as vehicles to deliver the correct gene and/or produce functional protein. Early gene editing studies using CRISPR/Cas9 also give hope for future therapies.

The types of gene therapy studies can be divided into four categories:

1. **Integrating gene therapy.** A correct version of the CFTR gene becomes a permanent part of the genome. CAR-T therapy, used to treat certain types of lymphoma and leukemia, are considered integrating gene therapy.
2. **Non-integrating gene therapy.** A new copy of the CFTR gene is delivered to a patient's cells but it does not become part of the genome. The cell uses the new copy to make functional CFTR proteins.
3. **RNA therapy.** The cell uses RNA to build the protein.
4. **Gene editing.** Instead of delivering a correct CFTR gene, CRISPR/Cas9 technology uses a piece of modified RNA to recognize and "cut" the targeted DNA sequence, removing the mutation, and allowing the cell to repair itself.

Gene editing comes with significant risks. A new mutation could develop if scientists cut the wrong sequence. In addition, gene editing relies on cell division. Most cells in adult lungs do not divide, which means gene editing may not be effective even if the correct sequence is removed.

Approach	Description	Potential Advantages	Potential Disadvantages
Integrating GT	A piece of DNA containing a new copy of the CFTR gene is delivered to the patient's cells and becomes a part of the patient's genome	Permanent change to the genome means that this treatment may be needed only once or very few times	Potential for side effects, such as an increased risk of cancer
Non-Integrating GT	A piece of DNA containing a new copy of the CFTR gene is delivered to the patient's cells, but remains separate from the genome	Does not disrupt the rest of the genome because the DNA is not integrated, meaning the risk of side effects is low	This process is not permanent, and the effects may be short-lived (weeks / months) meaning repeat dosing would be required over time
RNA Therapy	Copies of messenger RNA delivered and used to build functional CFTR proteins	Does not disrupt the genome because mRNA is not part of the genome	Effects may be short-lived and require repeat dosing over time
Gene Editing	A "tool," such as CRISPR, is used to locate the mutations in a patient's genes, cut out the mutations, and allow the cell to repair the DNA correctly	Permanent change to the genome means that this treatment may be needed only once or a very few times	Risks include the potential for edits made at incorrect locations in the genome. Potential for lack of efficacy due to a large number of CF-causing mutations and reliance on the cell's own machinery to repair the cut

CF Gene Therapy Clinical Trials: Considerations for Sponsors

While nearly all types of clinical trials benefit from patient-centric approaches, they are especially important in gene therapy trials. CF gene therapy studies require years of follow-up and involve multiple specialists, both of which create logistical challenges. In addition, because people with CF already have approved treatment options, sponsors will need to educate patients on the benefits of participating. Consider the following patient-centric practices when planning your CF gene therapy study.

- Develop clinically meaningful endpoints that matter. To help ensure endpoints are meaningful to researchers as well as patients, engage with the CF community early to seek input on endpoints and study design. Also, consider your population – are you targeting a specific age group or mutation?
- Get specialists in sync. A gene therapy trial involves multiple specialists, starting with a pulmonologist or pediatric pulmonologist as Principal Investigator. Make sure research sites have a plan to coordinate physician schedules to make site visits efficient for the patient. Your CRO should stay in close contact with sites to make sure appointments run smoothly.
- Work with a travel vendor. Clinical trial participants may not live close to a CF research center. Patients traveling to sites for gene therapy trials will likely need to stay at or near the site for up to three months. They will also need follow-up visits for several years. If the study involves pediatric patients, one or more family members and/or caregivers must travel with them.
- Travel vendors make participating as convenient as possible by coordinating travel, meals, lodging, and other logistics. They typically have IRB and EC regulation knowledge and can assist with both national and international travel. They also make sure patients are reimbursed promptly for any travel-related expenses and coordinate payment of stipends when applicable.
- Network with patient advocacy groups. Close relationships with advocacy groups can make the difference between meeting recruitment goals and a derailed trial. For patients, gene therapy is unfamiliar, risky territory. Advocacy groups educate patients on the value of participating in clinical trials — including yours. For a CF study, the Cystic Fibrosis Foundation and Emily's Entourage are great places to start.
- Use technology when possible. Telemedicine, home health nurses, electronic patient-reported outcomes (ePRO), and other tools further reduce patient burden by eliminating unnecessary travel and burden. While in-person site visits will be necessary in most cases, using remote options where possible can help lower travel costs and the incidence of dropouts.

Conclusion

Gene therapy research is generating excitement in the CF community. When designing a CF gene therapy trial, consider patient needs early and often for the best chance of success. For a seamless process, partner with a CRO that has gene therapy experience and close relationships to the CF patient community.

To learn more or to schedule a meeting, please Contact us today.

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