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Cystic Fibrosis Research News

Title:

Antisense oligonucleotide-based drug development for Cystic Fibrosis patients carrying the 3849+10kb C-to-T splicing mutation

Lay Title:

Drug development for Cystic Fibrosis patients carrying the 3849+10kb C-to-T splicing mutation

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What was your research question?

To develop a new therapy for cystic fibrosis patients carrying the 3849+10kb C-to-T splicing mutation, using molecules termed antisense oligonucleotides that can be designed to correct this specific mutation.

Why is this important?

When cells read the gene to produce CFTR, they need to make a copy of the gene and then remove the unnecessary parts of the code. This is achieved by splicing out sections of the copy. The 3849+10kb C-to-T mutation causes this to fail and not produce a correct CFTR.
The 3849+10kb C-to-T defect is the 7th most common CFTR defect in the US and 8th in Europe, carried by ~1600 CF patients. In several populations, the mutation is highly prevalent, such as in Ashkenazi Jews and CF patients in Slovenia, Poland and Italy. The current available CFTR modulators have only a limited clinical benefit for patients carrying splicing mutations including the 3849+10kb C-to-T mutation. Thus, further strategies of drug development are essential to address the unmet needs of patients carrying this mutation.

What did you do?

To correct the splicing of the CFTR gene with 3849+10kb C-T mutation, we designed antisense oligonucleotides that are complementary to specific sequences along the CFTR gene carrying this mutation and can influence the splicing of the gene copy. We screened ~30 antisense molecules. The effect of highly potent candidate molecules on the CFTR RNA processing and protein function was further analysed in human respiratory cells, derived from various patients carrying at least one copy of the 3849+10kb C-to-T mutation. We were able to efficiently deliver the antisense oligonucleotides into the cells directly, without any carriers. In addition, we tried molecules with varying chemical structures to identify the most efficient and potent molecule.

What did you find?

Following comprehensive analyses, in various cellular systems, we have identified a lead drug candidate, able to correct the aberrant CFTR splicing and restore normal protein function in respiratory cells from patients carrying the 3849+10kb C-to-T defect. Optimized efficiency was further obtained using different chemical structures of the molecule. The lead drug candidate was highly effective and potent and was able to restore the CFTR channel function to levels expected to confer a significant clinical benefit, and improved quality of life for patients carrying this defect.

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What does this mean and reasons for caution?

Our strategy led to a new therapy that can generate normal CFTR protein and restore CFTR function in cells from patients carrying the 3849+10kb C-to-T mutation. Given the limited clinical benefit of the currently available CFTR modulators for these people, our new therapy has significant clinical potential to patients with the 3849+10kb C-to-T mutation.

What's next?

We are progressing towards a clinical trial, recruiting patients who carry at least one copy of the 3849+10kb C-T mutation. We are aiming to implement our strategy on additional CFTR defects affecting correct splicing. We believe that this therapeutic strategy will have a significant benefit for all these patients.

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