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Cystic Fibrosis Research News

Title:
Antisense oligonucleotide splicing modulation as a novel Cystic Fibrosis therapeutic approach for the W1282X nonsense mutation

Lay Title:
Antisense oligonucleotide as a novel therapy for people with CF affected by the W1282X mutation

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What was your research question?
Can antisense oligonucleotides (ASOs) help to bypass the W1282X mutation and thereby avoid RNA degradation, which allows production of CFTR proteins which are partially active?

Why is this important?
Recent development of CFTR modulators to increase quantity and function of the CFTR proteins have been approved for some CF-causing mutations. However, they are not effective for all people with CF leaving an unmet need for drug development for people with non-responsive CFTR mutations. These mutations include a group called nonsense mutations that cause degradation of the RNA carrying the mutation and lead to the production of low levels of truncated CFTR proteins. We focus on a nonsense mutation, W1282X, one of the ten most prevalent CFTR mutations that is associated with a severe CF disease form for which there is no available therapy.

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What did you do?

We thus screened ~80 ASO candidates to find which helped efficiently bypassing the W1282X mutation. ASO candidates which showed significant effect were assessed for their ability to increase CFTR protein formation and function. The effect of highly potent ASO candidates was further analysed in human nasal cells, derived from a person with CF that has two W1282X mutations.

We verified the specificity of highly potent ASOs to the mutation, which is important for people carrying one copy of the W1282X mutation and one other CFTR mutation, to ensure a minimal effect on the non-W1282X mutation.

What did you find?

We identified several ASOs that worked efficiently. As a result, partially active CFTR proteins were produced and together with the CFTR modulator elexacaftor/tezacaftor/ivacaftor (Trikafta) the channel function of the CFTR proteins was restored. The most potent ASOs were also efficiently delivered to respiratory cells from a person with CF that has two W1282X mutations, promoted production of CFTR proteins and restored CFTR function.

Importantly, the most potent candidate ASOs showed high specificity for W1282X both on RNA and protein levels.

What does this mean and reasons for caution?

The effects of the lead ASOs demonstrate that ASOs have therapeutic potential for people with CF carrying the W1282X mutation. The use of ASOs is highly specific allowing manipulation of only the designated mutation which avoid off target effects and minimize side effects.

What's next?

We are currently further developing the most potent ASO candidate SPL23-2 for inhalation, to a proof-of-concept study in people with CF that have the W1282X nonsense mutation .

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