Antisense Therapy for Duchenne Dystrophy

There is no known cure for muscular dystrophy, although significant headway is being made with antisense oligonucleotides.

Duchenne muscular dystrophy is caused by a nonsense mutation (nmDMD)

First let us see a normal DNA sequence leading to a normal m-RNA and a normal protein as shown in Fig 1 below:

DNA: 5' - ATG ACT CAC CGA GCG CGA AGC TGA - 3'

3' - TAC TGA GTG GCT CGC GCT TCG ACT - 5'

mRNA:5' - AUG ACU CAC CGA GCG CGA AGC UGA - 3'

Protein: Met Thr His Arg Ala Arg Ser Stop

Fig 1 – Normal Translation into an effective protein.

Suppose that a nonsense mutation was introduced at the fourth triplet in the DNA sequence -CGA-causing the cytosine to be replaced with thymine, yielding TGA in the DNA sequence(See Fig-2).

Since TGA is transcribed-then-translated as UGA, the resulting transcript and protein product would be short in sequence and ineffective :

DNA: 5' - ATG ACT CAC TGA GCG CGA AGC TGA - 3'

3' - TAC TGA GTG ACT CGC GCT TCG ACT - 5'

mRNA:5' -AUG ACU CAC UGA GCG CGU AGC UGA - 3'

Protein: Met Thr His Stop

Fig-2 Abnormal translation with early stop signal producing an ineffective protein .

The remaining codons of the mRNA are not translated into amino proteins because the stop codon is prematurely reached during translation. This can yield a truncated abbreviated protein product, which quite often lacks the functionality of the normal, non-mutant protein.

Antisense therapy is a novel, orally administered small-molecule compound for the treatment of patients with genetic disorders due to a nonsense mutation.

It is a form of treatment for genetic disorders. When the genetic sequence of a particular gene is known to be causative of a particular disease, it is possible to synthesize a strand of nucleic acid (DNA, RNA or a chemical analogue) that will bind to the messenger RNA (mRNA) produced by that gene and inactivate it, effectively turning that gene "off". This is because mRNA has to be single stranded for it to be translated.

Alternatively, the strand might be targeted to bind a splicing site on pre-mRNA and modify the exon content of an mRNA.

This synthesized nucleic acid is termed an "anti-sense" oligonucleotide (ASO) because its base sequence is complementary to the gene's messenger RNA (mRNA), which is called the "sense" sequence (so that a sense segment of mRNA " 5'-AAGGUC-3' " would be blocked by the anti-sense mRNA segment " 3' UUCCAG-5' ").

2 well known anti-sense therapy are listed below:

1-Ataluren makes RNA less sensitive to premature stop codons (referred to as "read-through"). This may be beneficial in diseases such as Duchenne muscular dystrophy where the mRNA contains a mutation causing premature stop codons or nonsense codons.See Fig-3

2-Lumacaftor, targeting the F508del mutation for patients with cystic fibrosis

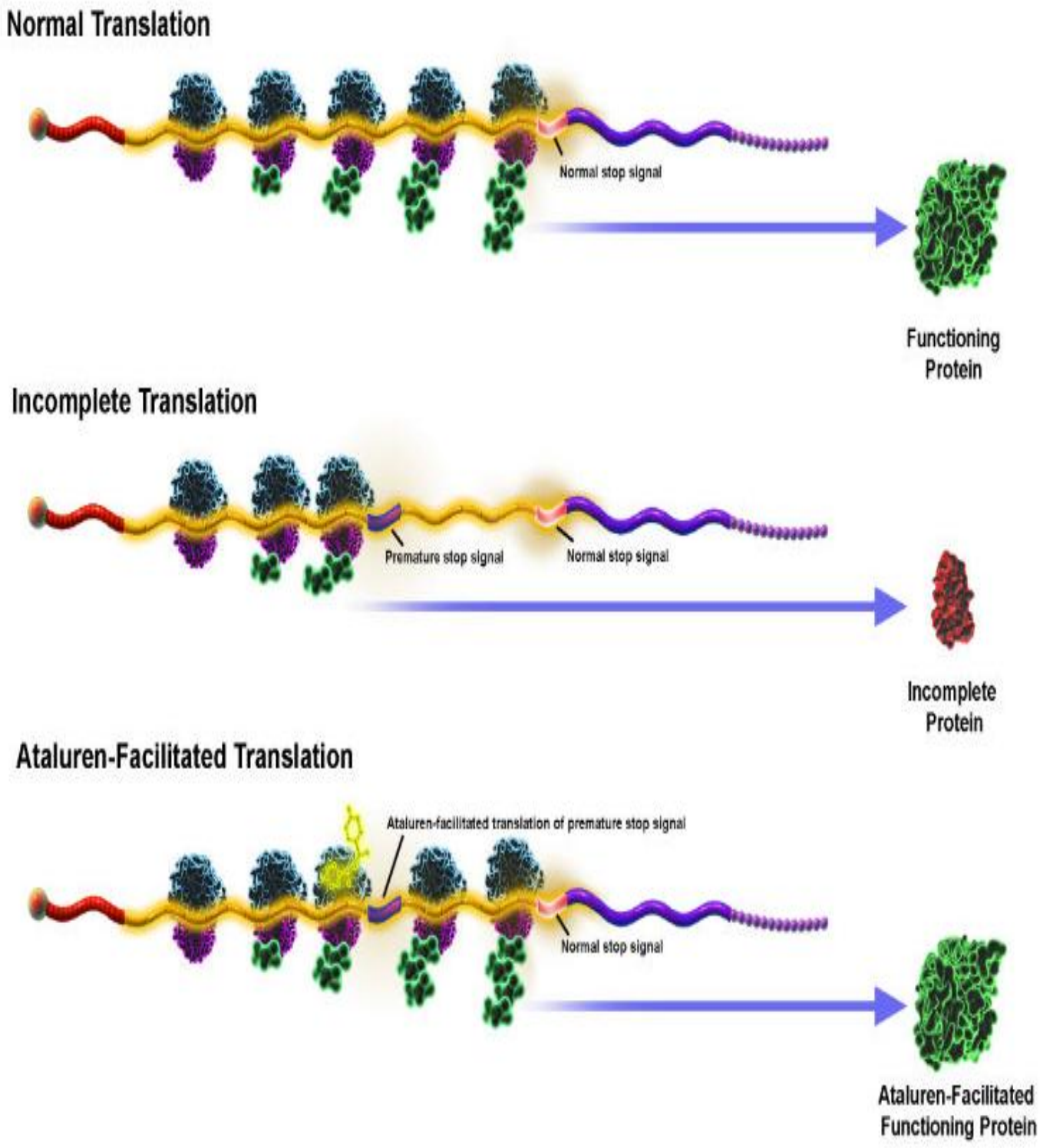

Fig-3. Translation of an mRNA into protein: comparison of normal translation, premature termination of translation, and treatment with Ataluren inducing synthesis of functioning protein.

In August 2014, ataluren received market authorization from the European Commission to treat patients with nonsense mutation Duchenne muscular dystrophy. A confirmatory phase III clinical trial is ongoing.

Ataluren proved effective treatment of patients with nonsense mutation dystrophinopathy as published in The journal **Muscle Nerve**. 2014 Oct;50(4):477-87

The drug does not yet have approval by the US Food and Drug Administration.

The most common adverse reactions experienced by patients who received Ataluren in the pooled placebo-controlled Phase 3 studies were mild and included abdominal pain (15.6% versus 12.5% on placebo), diarrhoea (12.8% versus 9.6% on placebo), dizziness (9.2% versus 1.0% on placebo), rash (12.8% versus 6.7% on placebo) and upper respiratory tract reactions.

Prognosis depends on the individual form of muscular dystrophy. In some cases a person with a muscle disease will get progressively weaker to the extent that it shortens life span due to heart and breathing complications. However, some of the muscle diseases do not affect life expectancy at all. There is a tremendous amount of ongoing research to find cures and treatments to slow muscle weakness. There is also a lot of research to learn how best to manage the breathing and heart issues which generally impact lifespan more than the muscle weakness.

A glimpse of Hope is in the horizon.

Edited by Dr Ghassan George Haddad

American Board of Psychiatry and Neurology