

## Lay Summary for the COST Action BM1207 funded meeting on translational and regulatory challenges for exon skipping therapies

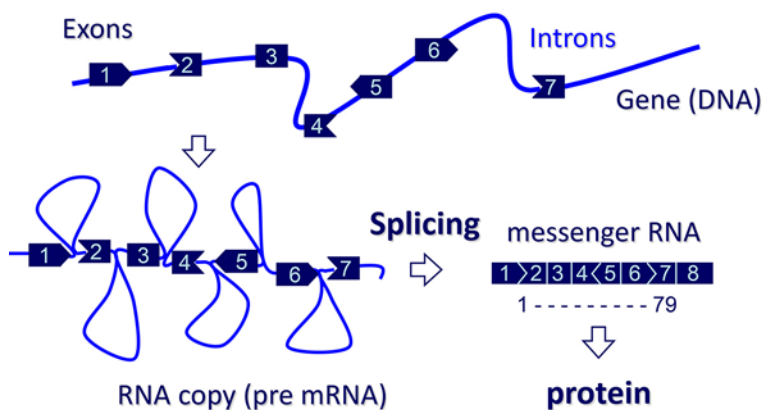
Antisense-mediated exon skipping is an approach that may have therapeutic potential for rare diseases. However, several challenges currently impede the development of this approach.

Some of these challenges are caused by the fact that for rare diseases patient numbers are small which makes it more difficult to study the disease and do clinical trials compared to common diseases. As a consequence, for many rare diseases no treatment is yet available, and thus there is often only limited expertise with conducting clinical trials and clinical outcome measures.

However, there are also challenges specific to the antisense-mediated exon skipping approach. These were the focus of a recently held workshop funded by the Cooperation of Science and Technology (COST).

### *What is antisense-mediated exon skipping*

Our body consists of >100,000 different proteins. The blueprint for these proteins lies in our genes; each gene contains the genetic code for one or more proteins.



Genes consist of DNA and contain the genetic code for proteins. This code is dispersed over exons, while introns that lie between exons do not contain protein information (Figure, top). When a protein needs to be produced, a temporary transcript (RNA) is produced (Figure bottom left). Before the transcript can be translated into protein, first the pieces not containing protein information have to be removed. This occurs in a process called splicing that cuts out the introns and links together all the exons. This leads to a 'messenger RNA' transcript that can be translated into a protein (Figure bottom right).

Genetic mutations underlie many inherited rare diseases. When an error (mutation) occurs in a gene, this error will be copied in the RNA transcript and translated into a mutated protein that is often not functional. However, mutations can also disrupt the splicing process; it is estimated that ~15% of genetic mutations cause the splicing to go wrong, e.g. a piece of intron can be included into the messenger RNA (making the genetic code unreadable), or the genetic code can be disrupted because exons are not recognized.

Antisense oligonucleotides (AONs) are small pieces of modified DNA that can specifically bind to RNA transcripts and in this manner mask part of the transcript from the machinery involved in the splicing process. In this way it can for example prevent a piece of intron from being included (so a normal protein can be formed), or the genetic code can be restored (so allowing the production of a partially functional protein).

#### *Antisense oligonucleotide specific challenges*

Antisense-mediated exon skipping and other therapies with AONs are new approaches and therefore only limited information is available on long term safety and toxicity of AONs. Furthermore, AONs are often mutation-specific, meaning they often apply to a subgroup of patients with a rare disease (so even smaller numbers of patients).

#### *The regulatory process*

The regulatory process is in place to ensure that only drugs that are effective and are safe are approved. When evaluating whether a drug is effective, regulators take into account whether the drug leads to a clear benefit for the patients, what are its side effects and what the severity of the disease is (i.e. what happens when patients are not treated?). Based on this information, they will make a 'benefit/risk' analysis, taking the severity of the disease into account, where the positive effects of the drug (e.g. less symptoms, slower disease progression) are balanced against the side effects of the drug.

#### *Different type of marketing authorization*

In Europe approval for drugs for rare diseases is centralized via the European medicine agency (EMA). There are different types of marketing authorization that provide access to the EU marketing and are available for companies or academia developing new drugs to apply for. A full marketing authorization is the standard type, which requires a comprehensive amount of information on clinical benefit and safety for the drug in question. For rare diseases it can be difficult to obtain "the standard" amount of data due to the limited patient numbers.

Conditional marketing authorization is a mechanism for drugs that treat severe and/or rare, life threatening diseases for which no appropriate treatment is available. For this type of authorization the amount of information needed at the time of the granting still must be sufficient to allow the regulators to perform a benefit/risk analysis and conclude that the benefits outweigh the risks, but these data could be less than "the standard". For conditional approval, the additional data that would be required for full marketing authorization can be collected AFTER the approval has been obtained. The approval is conditional, on the basis of the collection of further data and the benefit/risk balance is re-evaluated on a yearly basis. Once all the required additional data have been gathered, the drug can receive full marketing authorization (provided the benefit/risk evaluation is still positive). The legal basis of this approach allows for drugs to be taken off the marketing if the evaluation of additional data reveals that the benefit/risk ratio is no longer positive.

For rare, debilitating and life-threatening diseases, EMA recently set up a pilot program on adaptive licencing. This is a process where a drug is authorized early for a restricted group of patients (e.g. a certain age range, or disease stage) based on data that show strong trends for clinical benefit in the

absence of safety issues. When additional information is obtained in additional groups (e.g. another age range or disease stage), the licensing can become wider.

For very rare diseases, where comprehensive data will never be available, marketing under exceptional circumstances can be used. This is restricted to situations where it is impossible to acquire information in clinical trials to use the other models for marketing authorization (e.g. due to a very limited patient populations). Here, yearly evaluation of the benefit/risk ratio will be done (like with conditional marketing authorization).

#### *Compassionate use*

Patients can gain early access to drugs that have not yet obtained marketing authorization through compassionate use programs. This mechanism only applies to drugs that are in the development stage or subject of a marketing authorization procedure. Regulations for compassionate use differ per country (e.g. who is responsible, who reimburses the costs and how adverse events and/or efficacy are measured). Compassionate use can only be provided if there is a reason to believe the drug in question would be beneficial to a group of patients not included in the clinical trial ongoing to test the safety and efficacy of the drug. Once marketing authorization is obtained in EU countries, compassionate use is no longer an option in these countries.

#### *Aim of the workshop*

To discuss the challenges for developing antisense-mediated exon skipping for rare diseases, a workshop focusing on preclinical development, trial design, outcome measures and different forms of approval was organized by the regulatory models and biochemical outcome measures working groups of Cooperation of Science and Technology (COST) Action “Networking towards clinical application of antisense-mediated exon skipping for rare diseases” ([www.exonskipping.eu](http://www.exonskipping.eu)). The workshop included participants from patient organisations, academia and members of staff from the European Medicine Agency and MEB.

#### *Outcomes of the workshop*

- Defining ‘clinical benefit’ for diseases is difficult for diseases lacking a treatment. Patients and clinicians will have to discuss this at an early stage of drug development with regulators, because it is important to know this for the regulatory process
- What is considered ‘clinical benefit’ may differ for different disease stages (e.g. ambulant patients vs patients in a wheelchair). This should be taken into account.
- Generally a clinical outcome measure is used as a ‘primary endpoint’ to test whether a drug leads to clinical benefit (e.g. a test for muscle function for muscular dystrophies). Biomarkers can be used as surrogate endpoints to allow shorter trials. However, they first have to be validated and qualified to show that they correlate with clinical benefit. This is a lengthy process. More information on biomarkers and surrogate endpoints for Duchenne muscular dystrophy can be found [here](#)
- It is important to have detailed information on the disease course (e.g. from natural history studies) to
  - Identify what good outcome measures are to detect clinical benefit
  - To plan trials well

- Ensure appropriate patients are selected in trials who represent the real life situation, but inclusion of whom also is expected to provide meaningful information on the efficacy and/or safety of the drug
- To identify what clinical benefit is for the disease or disease stage

If no data are yet available it is crucial to start collecting this, because ideally it should be available before the onset of clinical trials

- Because exon skipping AONs are a new type of drug, at the moment placebo-controlled trials are needed to assess safety and efficacy. Should an AON receive approval for a certain disease, it may be possible in the future to do trials without a placebo group for additional AONs for that disease. Lacking information on long-term safety for exon skipping AONs, as yet, means that class approval of AONs or a certain AON chemistry is unlikely.
- Sometimes more than one AON needs to be used (e.g. when 2 exons need to be skipped). This is not simply a matter of giving 2 approved AONs to patients (should these become available). It will be crucial to show that combining the AONs is safe and the dose of the individual AONs will have to be optimized (e.g. double doses may lead to safety concerns, while lowering the dose of each AON may not be effective)

In summary, the workshop identified the current and future challenges in gaining marketing authorization for antisense-mediated exon skipping drugs for rare diseases.