Q&A: Defeat Duchenne Family Forum – Montréal

Answered by Dr. Jacques P. Tremblay, Laval University

From: Wednesday, May 20, 2020

Questions Received in English:

1. From Vincent: is the cost of CRISPR affordable?

The cost of CRISPR based therapy will be similar to the other gene therapies. The main cost of gene therapy is currently the production of AAVs in Good Manufacturing Practice (GMP) conditions. Thus I think that the main way of reducing the cost of gene therapy (delivery of a normal gene to compensate for a mutated gene) and of gene correction using CRISPR derived gene therapy is to develop alternative methods to deliver the treatment. There are two alternative methods to AAV: 1) extra-cellular vesicles derived from human plasma or from the culture medium of cells in culture or 2) nanoparticles made by chemists. These two methods are being investigated by many groups.

2. From Jaldeep: Thank you so much for a wonderful presentation, very informative. Most of the treatment options you mentioned are for later mutations e.g. 50 onwards, what about missing 21 - 22 exon? What are our options?

I think that there are two possibilities: 1) the transplantation of myoblasts obtained from a normal donor since they will contain axons 21 and 22. This is a solution for all mutations in the dystrophin gene. The main problem with that therapeutic approach is that this treatment require many injections in each muscle thus this is a very invasive procedure. The other alternative that I have mentioned is the possibility of inserting the two missing exons fused together in intron 20. This is a new possibility using transposases guided by the CRISPR technology (Halpin-Healy et al. Nature 2020).

3. From Rachael: Thank you Dr. Trembley. I have some hope for Cullen. I am concerned about the costs of potential treatments.

I am also worry about the cost of treatments. There is two reasons for these high cost. 1) The production of some of the components of the treatments is very expensive. 2) The companies that do the clinical trials want to recover the cost of only the clinical trials that led to the treatment but also of many other clinical trials that were not successful.

Personally I think that governments should pay for the clinical trials. However, this is a dream since currently governments do not invest enough I research to cover the cost of pre-clinical research and researchers are dependent on grants from private foundations, such as Jesse Journey.

4. From Michiel: Are research studies being carried out on multiexon deletions in other regions such as exon 6 to 16.

As mention in my answer to question 2, there is new research on the possibility of inserting one exon or several exons fused together at a specific site in the genome. This type of research is new and is derived from the CRISPR technology that does not stop to surprise us with all the new possibilities.

5. From Rachael: Do you have any idea when human clinical trials may happen for CRISPR technology?

The web site clinical trial.gov is a web site maintained by the National Institute of Health (NIH). There is a list of all clinical trials. I was surprise to find that there is a list of 21 trials when I have entered the term 'CRISPR'. These clinical trials are on the treatment of Sickle Cell Disease, leukemia, cancer, HIV, tuberculosis, Thalassemia and Leber Congenital blindness. Thus some phase I clinical trials have started.

6. From Paul: Has Dr. Olson started any human trials with his CRISPR? When is that expected?

Dr. Olson has not yet started a clinical trial with CRISPR. However, his first trial will probably be on the skipping on exon 51 as many other clinical trials using antisense oligonucleotides to induce the skipping.

7. From Andrea: What has happened to utrophin upregulation research? That would also benefit all types of mutations causing Duchenne. Thank you for this great presentation.

A good web site to find what is going on in research is https://www.ncbi.nlm.nih.gov/pubmed By entering 'utrophin Duchenne Muscular Dystrophy' in the search bar I found 565 articles on this subject! Twelve of these articles are in 2020. In the web site clinical trial.gov I found only one completed clinical trial with a drug SMT C1100 (ezutromid) that up-regulates utrophin. The table of results is difficult to interpret!

8. From Michiel: Are any of the transplantation studies taking place in Canada?

The myoblast transplantation study is done in London (Ontario) by Dr. Craig Campbell.

9. From Patrick: Does Dr Tremblay have a succession plan to continue the research he is working on?

UNFORTUNATELY, the recruitment of a professor in a university department is very complex and at this point I do not have a successor. However, I am still in very good health and I do not plan to retire soon. Anyway, since the results of my research are published, successors will appear anywhere in the world!

Questions Received in French:

10. From Ann-Marie: Est-ce que le saut d'Exon (Vyondys 53) est plus efficace que prendre des corticostéroïdes?

Les corticostéroïdes sont un traitement pour tous les patients DMD tandis que le saut de l'exon 53 est une solution pour seulement certains patients. Pour les patients qui peuvent être traités avec Vyondys 53, je pense que ce traitement est une meilleure option.

11. From Véronique: POur une personne atteinte de Duchenne ayant 15 ou 20 ans (âge plus avancé) pourrait-il recevoir ce traitement et permette l'amélioration de ces capacités physiques?

Pour l'instant, mon groupe de recherche a démontré dans un essai clinique de phase I que la greffe de myoblastes a permis d'obtenir l'expression de dystrophine dans dans fibres musculaires dans le muscle qui a reçu la greffe. Dans des souris et dans les muscles de ces patients, nous avons pu observer la présence de nouvelles petites fibres musculaires. Cependant nous ne savons pas si ces petites fibres musculaires augmentent progressivement de grosseur et pourraient éventuellement augmenter la force du patient.

12. From Colette: est-ce qu'une duplication d'exon est traité de façon similaire à un saut (delation)?

À ma connaissance, une duplication ne pas être traitée par saut d'exon parce qu'on éliminerait les deux copies de l'exon. Cependant, un group italien, Lattanzi et al. Molecular Therapy Nucleic Acid 2017 (voir https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5363679/) a fait une expérience avec des myoblastes provenant de deux patients ayant une duplication de l'exon 2. Ils ont induit une coupure avec CRISPR à l'intérieur de l'exon 2. Il y a donc eu une coupure dans le premier exon 2 et dans le deuxième exon 2. La séquence de nucléotides entre les deux sites de coupure a été éliminée. Il y a eu formation d'un seul exon 2 formé par le début du premier exon 2 et la fin du deuxième exon 2. L'expression de dystrophine a été rétablie dans de petites fibres musculaires en culture. Malheureusement, il ne semble pas que ce groupe italien a continué sur ce type d'expériences.

Jesse's Journey would like to thank Dr. Tremblay for speaking at the Defeat Duchenne Family Forum and kindly providing the answers to the participant questions after the event.

Thank you to all of the participants for engaging through the Q&A – we look forward to seeing you at the next event on Saturday, May 27, 2020!