**Cutting edge research at Ulster University – a novel treatment for inherited blinding eye diseases**

The cornea is the window at the front of the eye through which light passes allowing us to see clearly. Corneal dystrophies, which cause a loss of this essential transparency, are a group of inherited blinding eye diseases for which there is no cure. They worsen through life until sight is lost; medical care at most will address discomfort and pain but the only treatment option available is corneal transplant offered only when vision is almost lost. Transplant surgery often fails due to recurrence of the disease.

The Moore and Nesbit group, at Ulster University in Northern Ireland, is developing a new approach to treating these diseases before sight is lost using a novel gene-editing technology to correct the mistake in the DNA of the patient’s eye cells.

Patients with these type of inherited diseases often only have one single letter mistake in one copy of one of their 25,000 genes. Remember we get one from Mum and one from Dad. The gene from one patent works perfectly well, but the damaged copy takes priority over the normal copy, it dominates- hence these types of diseases referred to as dominantly inherited diseases and they can affect various parts of the body, not just our eyes,

Ulster University researchers aim to remove the damaged copy, leaving only the normal copy, restoring vision in these patients.

The same approach, once developed, can be applied to other diseases with similar dominant inheritance pattern such as Huntington's disease and neurofibromatosis.

We do this using an exciting tool, known as CRISPR/Cas9, which makes gene editing a realistic achievement in the clinic. CRISPR/Cas9 acts like a pair of molecular scissors that can be guided very precisely to cut at the exact place in all the 3 billion letters that make up the DNA in our cells.

CRISPR/Cas9 protein works its way along the DNA molecules, scanning until it finds a short 3 letter signal sequence that it must bind to. It then looks at adjacent 18-20 letters to see whether they match the sequence that you have given it to look for. If the molecular scissors i) find the correct 3 letter signal and ii) finds the matching adjacent sequence, the scissors will cut the DNA- in our case the bad gene

Ulster Researchers in the Moore and Nesbit laboratory are able to utilise this system to direct the molecular scissors to cut the gene responsible for a patients’ corneal dystrophy.

Whilst doing this they must make sure the scissors only cut the gene with the mistake and leave the good gene uncut,

For the majority of corneal dystrophies, the only difference between the damaged and working copy of the gene is a single letter. PhD Researcher Kathleen Christie has performed experiments to investigate whether CRISPR/Cas9 could tell the difference between the damaged and the good gene and assessed if this single letter change could be more efficiently found in i) the 3 letter signal motif or ii) the 18-20 letter guide supplied to the molecular scissors.

They have reported that a significant proportion of corneal dystrophy mutations are found in neither the signal nor the guide sequence, while some are found in both and some in only one. Therefore, for the genetic causes that do have a mutation present in either position they tested whether the CRISPR/Cas9 molecular scissors could tell the difference between the damaged and undamaged copy of the gene.

Interestingly they found that if the single letter change was present in the 18-20 letter guide supplied to the molecular scissors, their gene therapy treatment was not able to discriminate between the damaged and undamaged copies of the gene, therefore could never translate to the clinic. However, if the single letter change, the disease causing mutation, was present in the 3 letter signal detected by the molecular scissors then in complete discrimination was achievable.

Since not all disease causing DNA damage will have the change of letter present in a signal motif, their current research involves expanding this approach to ensure targeting of the damaged copy in every case.

This novel gene-editing approach offers a single, permanent treatment option that will restore vision in these patients and importantly this research team are the first to obtain proof of concept in vivo- in living animals.

Most excitingly their tremendous leaps forward using the eye for this novel treatment will allow it to be expanded to other human diseases and impact upon the lives of so many suffering from genetic diseases, which currently have no other medical treatment capable of stopping these diseases from developing.