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Potential treatments for rare diseases: Cell therapy, gene therapy and genome editing

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All hereditary diseases are due to modification in the patient genome insertion, deletion or modification of one or several nucleotides among the 6 billion nucleotides of the human genome. Several potential therapeutic approaches to treat these hereditary diseases have been developed over the years. For some recessive diseases the transplantation of allogenic cells obtained from a healthy donor can permit to deliver the normal gene to compensate for the mutated gene. This approach is under clinical trial for Duchenne Muscular Dystrophy. A compensatory normal gene to treat a recessive hereditary disease may also be introduced in the patient own cells in culture or directly *in vivo* by using viral vectors. The Adeno Associated Viruses (AAV), are currently the vectors of choice for such a therapeutic approaches. Various specific nucleases (meganucleases, Zinc Finger Nucleases, TALENs and the CRISPR/Cas9 system) have been investigated during the lasts 10 years and now permit to precisely correct a gene responsible for a hereditary disease. This type of approaches is the only one that can be used for dominant diseases. This approach may also be used to correct large genes, which are too big to be delivered by AAV. My team and several others have already used this approach to correct the dystrophin gene, as a treatment for Duchenne Muscular Dystrophy. Indeed by using these specific nucleases, it is possible to induce double strands breaks in the dystrophin gene to restore the normal reading frame by micro-insertions, micro-deletions or by deleting complete exons or parts of exons. My team is also attempting to restore a completely normal dystrophin protein by inserting the exons, which are missing in the patient genome. My team has also been able to remove with the CRISPR/Cas9 system the long trinucleotide repeat in intron 1 of the frataxin gene responsible for Friedreich ataxia and thus increase the expression of frataxin in patient cells. The TALE proteins and a defective Cas9 nuclease (dCas9) may also be fused with a transcription activation domain, such as VP64, to target a gene promoter to increase specifically the expression of that gene. My team has successfully used that approach in cells of Friedreich patients. The CRISPR/Cas9 technology may also be used to correct a gene by a process called homology directed repair. This technique permits to modify one or several nucleotides in the whole human genome. Thus the progress in cell therapy, gene therapy and genome editing permits to dream of developing therapies for all hereditary diseases over the coming years. The main limiting factor is the financial support for this type of research.

Biography

Jacques P Tremblay has completed his PhD in Neurosciences in 1974 at University of California at San Diego. He has published 261 articles in peer-reviewed journals and has been serving as Deputy Editor of Molecular Therapy and Cell Transplantation. His laboratory is currently working on cell and gene therapies for Duchenne muscular dystrophy, Friedreich ataxia and Alzheimer disease.

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