**Use of Gene Editing to Treat Inherited Diseases**

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Techniques for precise editing of the human genome have emerged in the past decade. Gene editing may be used to correct pathogenic mutations for many diseases. The major technical advance that is enabling effective gene editing is the development of "designer nucleases" that can be directed to introduce a DNA double-stranded break (DSB) (ideally) at a single site in the human genome. Zinc finger nucleases, TALENs and, more recently, CRISPR/Cas9 are exquisitely site-specific endonucleases. They can stimulate gene editing by thousand-folds, by inducing the activity of endogenous DNA DSB repair mechanisms. We focus on gene editing in hematopoietic stem cells (HSC) for genetic blood cell diseases, and examples from that area will be used. Gene editing of autologous HSC and transplantation may provide safe and effective therapies for primary immune deficiencies, hemoglobinopathes, storage and metabolic diseases, as well as defects of HSC *per se*. Gene editing may be performed in isolated HSC in the lab by introducing the gene editing reagents (plasmids, mRNA, proteins) through electroporation or with transient viral vectors; the gene-edited HSC may then be reinfused for engraftment. Three major types of gene edits can be induced, depending on which DNA repair mechanism is used: gene disruption, gene correction and gene insertion. Gene Disruption can be achieved by introducing the gene editing nuclease into cells to produce a DSB at a target locus. The non-homologous end joining (NHEJ) repair pathway will re-connect the cut ends of the DNA, but will introduce variably-sized insertions and deletions (indels) at the joint; these indels disrupt the gene sequence and "knock-out" the gene. Clinical trials are evaluating the efficacy of disrupting the *CCR5* HIV-1 co-receptor to treat HIV-1 infection and the *BCL11a* transcription factor to induce production of fetal hemoglobin for beta-globinopathies. Gene Correction is performed by introducing both a nuclease to produce a targeted DSB, and also a "homologous donor template", which is a DNA sequence matching the target sequence but containing the sequence change to be introduced. The homology-directed repair (HDR) pathway can use the homologous donor template to direct the repair of the DSB and the sequence variations it carries will be inserted into the genome, editing-out the mutation. The uniform single base-pair transversion in the beta-globin gene causing sickle cell disease makes it an ideal target for gene correction in HSC. Relatively efficient correction of the sickle cell disease mutation has been achieved by several groups in pre-clinical studies with human HSC and is being advanced to clinical trials. Gene Insertion can be used to introduce entire genes into a specific target site. For example, a normal cDNA version of a gene can be inserted site-specifically into that target gene locus to be expressed from the endogenous control elements, *in situ*. Gene insertion can be used to over-ride any mutation in the gene and when the relevant gene needs to be expressed under regulated control. Translating these techniques to clinical applications in the setting of autologous hematopoietic stem cell transplantation is underway. Applications of gene editing for genetic diseases affecting other organ systems present the additional major challenge of *in vivo* delivery; novel nanotechnologies are being developed that may be capable of meeting this challenge. Gene editing provides unprecedented opportunities to truly cure genetic disorders and the applications are expected to expand.