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Editorial

Gene Therapy with CRISPR: Promising Outcomes and Potential Dangers

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EDITORIAL

Genetic engineering is seen as the ultimate answer to treat incurable diseases. Many researchers considered that analyzing abnormal genes, genetic mutations, or even engineering gene knockouts was just the beginning to assess how our genomes are regulated and function. However, learning how to read the genetic code does not give us the answer or ability to correct errors per se. Modifying the human genome has its obvious ethical issues and it has not been considered a safe solution until now. Scientists tried different approaches to safely correct the human genome using diverse techniques such as e.g. retroviral vectors, lentiviral vectors, adeno-associated virus, Chimeric Antigen Receptor (CAR) T cells, and morpholinos. But really modifying the genome is a completely different realm that became more auspicious with the possibility of gene editing techniques such as RNA interference (RNAi). RNAi has an immense potential to genetically down-regulate gene expression and recent results brought new hope to treat patients with Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA). However, a solution to rectify or change the genome of a patient with cancer, a rare genetic disease, or even immunological changes caused by HIV/AIDS brings a completely different level of complexity and inherent danger.

One of the major breakthroughs occurred during the last decade and it was achieved while studying how the bacteria adaptive immunity is able to neutralize viruses using CRISPR (clustered regularly interspaced palindromic repeats) and their associated proteins (Cas). The CRISPR/Cas system is in principle similar to the RNA interference used by eukaryotic cells as they both use short RNA sequences to guide the destruction of foreign DNA by enzymes. Assuming we fully understand the sequence we want to correct we still need to assure the targeting is completely reliable and there aren't any off-target deletions. Gene therapy to correct well-known genetic mutations and diseases such as cancer is already being attempted but we must measure the efficacy and the inherent risks. The use of this controversial tool has the ability not only to correct mutations but to also create genetic changes that are passed down through generations. Cutting out specific portions of DNA and replacing it with new sequences, like a cut-and-paste function, giving scientists the ability to remove cancer-causing mutations from DNA and replace it with immune-enhanced DNA sequences.

After a long procedure to approve its use to treat human patients, scientists of the University of Pennsylvania initiated a clinical trial to treat two cancer patients using CRISPR to engineer immune cells, one suffering from multiple myeloma and another from sarcoma (ClinicalTrials.gov - Identifier: NCT03399448). The trial ' NY-ESO-1-redirected CRISPR (TCRendo and PD1) Edited T Cells (NYCE T Cells)' is a first-in-human trial proposed to test HLA-A*0201 restricted NY-ESO-1 redirected T cells with edited endogenous T cell receptor and PD-1. The method comprises isolating and engineering samples of T-cells (immune cells) from each patient using CRISPR to delete one gene and add another. This technique will give those patients' immune system the ability to respond to and battle cancer in their bodies. But this is just one example occurring in the US.

Several clinical trials using CRISPR are already taking place worldwide. There are clinical trials using CRISPR in Europe to treat patients with blood disorders sickle cell anemia or beta-thalassemia (ClinicalTrials.gov Identifier: NCT03655678). The trial 'A Safety and Efficacy Study Evaluating CTX001 in Subjects with Transfusion-Dependent β-Thalassemia' will evaluate the safety and efficacy of autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) using CTX001. China is also performing diverse clinical trials to treat several types of cancer and the initial results shall be obtained soon. But one of the breakthroughs astonishing the whole world at the moment is the promising results using CRISPR to treat patients with HIV/AIDS. The clinical trial initiated in 2017 will evaluate the response of patients with an HIV-1 infection when treated with CRISPR CCR5 modified CD34+ cells (ClinicalTrials.gov Identifier: NCT03164135-Safety of Transplantation of CRISPR CCR5 Modified CD34+ Cells in HIV-infected Subjects with Hematological Malignancies). However, researchers are concerned about the lack of clinical follow-up in Chinese studies to evaluate the CRISPR modifications in detail. Just as a brief reference that will need more in-depth confirmation, official reports of the clinical trials taking place in China in 2018 acknowledged about 86 adults

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had been known to have been treated using CRISPR gene editing and at least 19 out of 21 patients treated this year have died.

A very important note we could not ignore are the dangers of using CRISPR to modify the human genome. It is difficult to assure an absolutely precise and unique targeting without affecting adjacent or similar sequences anywhere else in the genome. This serious concern is being followed by scientists eager to develop new methods to detect the off-target effects of CRISPR. In addition, the abusive use of this gene-editing technique is also an oversensitive affair. The scientific community was in shock after learning that a Chinese scientist claimed he had impregnated a woman with embryos that had been edited to disable the genetic pathway HIV uses to infect cells. But a big question remains. Is it unethical to modify the human genome as a preventive measure, or shall researchers be limited to treating patients already suffering from a disease? The scientific community is aware that potentially un-ethical situations are likely to occur in the future since CRISPR brings hope to many people afraid of transmitting their hereditary disorders to their offspring, not to mention the dangers of unscrupulous genetic enhancements for personal gains.