BT5130 - Tissue Engineering - Assignment 3

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Question - Ethics involved in sickle cell gene therapy with CRISPR for clinical trials (ongoing) versus the actions of Dr. He, as a case study approving the actions of editing stem cells and introducing it back into the body but not directly editing embryos.

Answer - The clinical trial (CTX001) involving CRISPR-Cas9 for Sickle cell gene therapy are currently in Phase I/II of their trials [1]. Through CTX001, a patient's hematopoietic stem cells are edited to produce high levels of fetal hemoglobin (HbF) in red blood cells. This gene, active during gestation, is naturally shut down shortly after birth. CTX001 restores expression by altering the upstream regulatory pathway. If the therapy manages to edit ~5% of the patient's stem cells, this would eventually help in reducing the percentage of abnormal blood cells to below ~30% [2]. Also, the therapy targets only the affected cells, i.e., blood cells, and engineers those stem cells that are destined to become blood cells. Hence, all the cells are not replaced, therefore reducing the overall risk as compared to what will be observed when the embryos are engineered.
Apart from this advantage, there are several factors and ethical questions concerning hemapoietic cell transplantation (HCT), which includes the eligibility criteria for HCT in terms of severity of the disease and other factors, the timefram for HCT from a healthy sibling to the patient and whether pre-implantation diagnosis needs to be performed and so on. A few of these are discussed briefly by Nickel and Kamani [3].

On the other hand, Dr. He Jiankui genetically edited embryos which would alter all the cells in the adult organism. This treatment involed HIV-positive fathers and HIV-negative mothers where the CRISPR-Cas9 technology was used to induce a gene-edit during the *in vitro* fertilisation procedure. Although we know that the three babies that were born as a result of this experiment are now healthy, the idea of using humans for testing hypotheses was shocking and new. Also, Dr He was trying to reproduce the CCR5-Δ32 mutation, but he had only introduced a frameshift mutation that would make the CCR5 protein non-functional. Hence, the babies involved in the experiment were not really protected from HIV [4]. There are several conflicts of interest with this experiment, apart from the conventional ethical questions that were stated earlier. First, it is not

very clear if Dr He and his colleagues who were involved in the project had obtained full consent from the parents and the statements regarding the funding seem very ambiguous [5]. Second, when the germline is edited, it not only confers changes to the adult organism, but also the immediate and the forthcoming generations. Hence extremely specific regulations needs to be carefully considered. Third, the power of science is very vast and widespread that literally and theoretically anything (good and evil) can be achieved. This sort of a power over the fundamental nature of our own biology is dangerous and it is often best if we don't mess with it [6]. With all the above aspects in consideration, and keeping in mind the bright future that genome editing brings along with it, many countries have even permitted experiments using genome editing in nonviable embryo leftovers from IVF, or synthetically constructed embryos, both of which have their own moral questions [7].

In summary, while somatic gene editing affects only the patient (may be only a part of his/her cells), germline editing affects the organism's cells including their egg/sperm and subsequent generations, which means that unpredictable occurrences of recombination during reproductions would make it difficult to approve [8]. Also human genome editing, in the current scenario can safely be affordable by the wealthy, but the poor families will still have to see their family members suffer. We are dealing with 'governance' and 'self-governance' and the silver lining is truly in the hands of the scientific community.

References -

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