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Opinion

CRISPR Applications Versus the Ethical and Regulatory Concerns

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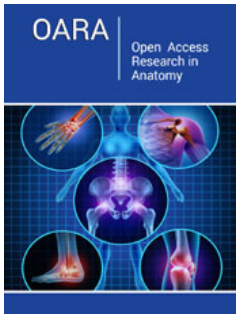

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Opinion

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has many applications such as editing the human genome and CRISPR-edited crops as well as CRISPR-edited animals for the use of human organ transplants [1-4]. However, are the applications of CRISPR ethically defensible or not? For simplification, I will go through one example, the CRISPR-edited animals for the use of human organ transplants, where CRISPR-gene editing solves the problem occurring with the traditional use of PSCs (Pluripotent Stem Cells) or iPSCs (Induced Pluripotent Stem Cells) to produce differentiated β-cells of pancreatic islets of Langerhans to treat type 1 diabetes and the subsequent fatigue of these transplanted stem cells and failure to produce insulin and recurrence of diabetes again. So, the best for treating Type 1 diabetes radically is to produce a physiologically active, and compatible artificial pancreas to be then transplanted to the patient, but iPSCs could not produce a whole pancreas *in vitro*. Accordingly, the idea evolved to implant the patient's pancreatic hiPSCs (human induced Pluripotent Stem Cells) into an adapted or humanized animal embryos to all the development of the human pancreatic stem cells into whole pancreas *in vivo* i.e., inside the humanized animal embryo.

This process will go through two steps; first is to implant hiPSCs into the blastocyst of the humanized animal (it is better here to be a pig to get an organ size big enough near to that of the human pancreas). Second is to create a pancreatogenesis-disabled blastocyst before being implanted by the hiPSCs to avoid the development of the pig's pancreas and instead the human pancreas will be developed. The production of the pig's pancreatogenesis-disabled blastocyst can be done by CRISPR-based gene editing by simply knocking-out (deleting) the genes responsible for the development of pig's pancreas. This could be done by relying on NHEJ (Non-Homologous End Joining) to delete these genes, rather than relying on HDR (Homology-Directed Repair) [5], which needs a template sequence which is not the matter in this process. Also, to prevent rejection of this pig-incubated human pancreas when transplanted to the patient (because of the pig-developed vascular supply to this pancreas during incubation), we need to develop or create a vascular-system-deficient pig embryo in which the hiPSCs will be injected to contribute in the development of the pig vascular system compatible with the required human pancreas, so not to be rejected when transplanted into the hiPSCs-donor human patient. To create this vascular-deficient pig embryos we can use CRISPR-based gene editing by deleting or knocking-out the genes responsible for the development of pig's vascular supply, by relying again on NHEJ rather than HDR. So, I could say yes to the use of humanized animals with utilizing CRISPR to produce transplantable human organs because of many he benefits. First, saving lives of the superior creature on earth-humans-where we can revise the statistics which stated that there are 22 organ transplant-waitlist patients die every day in the US alone, what about among the whole world [2]. This is of course against those who are crying for animal welfare and giving animals a sacrosanct level, which are not. And for those I would say that those chimeric experimental animals will be treated never like other animals, as they will be medically cared and will be treated mercifully during sacrificing them. Also, I would ask them, which is more priore, saving human lives as a whole or killing of millions of animals every day for getting meat, pork, poultry, fish, ...etc? [6].

Second, CRISPR-based gene editing can be used to limit or minimize the off-target risks and unintended or unwanted effects that may elaborate with gene editing. This can be achieved by limiting the differentiation capabilities of the implanted hiIPSCs by CRISPR-based targeting some maturation factors needed for full differentiation but not preventing it. Third, CRISPR-based genome editing can be used to develop a "Fail-safe mechanism" to limit or avoid off-target effects. Fourth, CRISPR-based genome editing can be used to introduce a "Suicide gene" to prevent or eliminate iPSCs differentiating to express neural differentiation markers, so, no brain or gametes would occur in the humanized chimeric animals used to incubate transplantable human organs. This is my answer against those who are contrary to CRISPR-based genome editing in the aforementioned procedure, who stated that the extensive use of hiPSCs in neural organs production may produce chimeric animals with high cognitive abilities similar or little pit near to the human ones, in addition to facial appearance, similar human limbs or even a possible cross-fertilization between humans and animals.

I would say that is not true to a big percent, because the off-target effects that may occur between very related species like rats and mice do not exceed 20%, as well as the interspecies barriers between humans and pigs are higher than those between rats and mice which concluding that using chimeric pigs would produce very low percent of the unwanted off-targets. Finally, and ethically, a global regulation should be assembled among researcher, institutions, industrial manufacturers and governments to weigh the major benefits CRISPR-based genome editing against the possible risks, and to oversight this technology not to reach to the hands of rogue, unauthorized or evil people and not to be used in bioweapons production [7].

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