The Science and Ethics of Human Genome Engineering

Overview and description of CRISPR-Cas9 technology

The rapidly expanding family of CRISPR-Cas9-derived technologies is revolutionizing the fields of genetics and molecular biology as researchers worldwide employ these methods to change DNA sequences – by introducing or correcting genetic mutations – in a wide variety of cells and organisms. The simplicity and efficiency of the CRISPR-Cas9 system enables any researcher with knowledge of molecular biology to modify genomes, making feasible many experiments that were previously difficult or impossible to conduct. The technology employs a bacterial protein, Cas9, that cuts specific DNA sequences defined by base pairing between a guide RNA molecule and a DNA target sequence. Researchers can easily alter the guide RNA sequence to direct Cas9 to desired sites in the genome of cells. The resulting double-stranded DNA break triggers site-specific sequence changes, enabling disruption or recoding of genes at will. Where older technologies were "hard-wired", requiring new proteins to be engineered for each experiment, the CRISPR-Cas9 system is analogous to software that is easily reprogrammable for a wide variety of experiments and functions across a broad range of plant and animal systems. For example, the CRISPR-Cas9 system enables introduction of DNA sequence changes that correct genetic defects in whole animals and cultured tissues produced from stem cells, strategies that could eventually be used to treat human disease. This technology can also be used to replicate precisely the genetic basis for human diseases in model organisms, leading to unprecedented insights into previously enigmatic disorders. For more information, see videos and references posted at www.innovativegenomics.org.

In addition to facilitating changes in differentiated somatic (adult) cells of animals and plants, CRISPR-Cas9 technology can also be used to change the DNA in the nuclei of reproductive cells that transmit information from one generation to the next (an organism's "germ line"). Thus, it is now possible to employ CRISPR-Cas9 for genome modification in fertilized animal eggs or embryos, thereby altering the genetic makeup of every differentiated cell in an organism and thus ensuring that the changes will be passed on to the organism's progeny. Humans are no exception - changes to the human germ line are now possible using this simple and widely available technology.

A prudent path forward for human germ line modification

The possibility of human germ line engineering has long been a source of both excitement and unease among the general public, especially in light of concerns about initiating a "slippery slope" from disease-curing applications toward uses with less compelling or even troubling implications. A key point of discussion is whether the treatment or cure of severe diseases in humans would be a responsible use of germ line genome engineering, and if so, under what circumstances. For example, would it be appropriate to use the technology to change a disease-causing genetic mutation to a sequence more typical among healthy people? Even this seemingly straightforward scenario raises serious concerns, including the potential for unintended consequences of heritable germ line modifications, since there are limits to our knowledge of human genetics, gene-environment interactions and the pathways of disease (including the interplay between one disease and the other conditions or diseases in the same patient).

In the United States, human research currently requires an Investigational New Drug (IND) exemption from the Food and Drug Administration, but some countries do not have such regulations in place. A recent Perspective that I co-authored advocated a halt to any clinical applications of human germ line editing until the safety, efficacy and ethical considerations of such use have been assessed (Baltimore et al. (2015) *Science*).

Legal and societal concerns around genome engineering

The CRISPR-Cas9 technology makes it easier and faster to introduce site-specific changes into the DNA of cells, tissues and whole organisms on a scale far beyond what has been possible in the past. Anyone with basic knowledge of molecular biology can employ this powerful technology, which makes regulation difficult. In addition, the versatility of the technology raises various scenarios that warrant careful consideration, review and oversight. Applications of genome engineering that create heritable changes in humans, introduce self-propagating mutations that sterilize insects or trigger chromosome translocations that cause cancer are examples that have already been published in the scientific literature and could raise both legal and societal concerns.

Towards a responsible framework for using genome editing technologies

The importance and complexity of the issues surrounding some applications of genome engineering methods warrant thoughtful review with a goal of crafting guidelines for responsible use. Towards this end, the National Academy of Sciences and the National Academy of Medicine are co-sponsoring forthcoming meetings and will commission formal reports to provide guidance to scientists, clinicians and regulatory agencies. These meetings will involve international participation by people representing different scientific organizations and points of view. Past experience with technologies such as molecular cloning, *in vitro* fertilization and embryonic stem cell manipulation should help inform the course of action taken.

US role in scientific and ethical leadership in this area of science

The US has three critical roles to play in creating a responsible framework for the use of genome engineering technologies. The first is to provide expert information and recommendations to the scientific community about the risks and benefits of genome engineering for various types of applications in humans, other mammals, and organisms including plants, insects and microbes. The second is to lead an international consortium of scientists and clinicians in drafting guidelines for use that will form the basis for regulation and oversight by governments worldwide, particularly for applications involving the human germ line. The consortium should also provide advice about other applications of genome editing that could impact the environment, food security and human health. And the third role the US should play is to educate the public about the benefits and risks of genome editing. This will enable non-scientists to understand the opportunities as well as the potential dangers of the technology and to make decisions about its use from an informed perspective.