

FANCY FINGERS IN GENE REPAIR: HUMAN GENOME ENGINEERING

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The human genome sequence information is the blue-print for the program of life, which guides biological development and function. The completion of a high-quality, comprehensive sequence of the human genome in 2003, which codes for about 30,000 genes, was a landmark event in the history of the scientific enterprise. The challenge then is to utilize this immense potential of human genome sequence to improve human health and well-being.

A robust and reproducible means of specifically correcting “faulty” bases (or introducing directed mutations) in genes has been a long sought-after goal in Genetic Medicine. Engineered Zinc Fingers Nucleases (ZFN) are becoming powerful research tools for highly efficient and permanent site-specific modification of various types of cells, organisms, plants and animals. It must be emphasized that the sequence-specificity and affinity of the engineered ZFNs are only as good as the Zinc Finger Proteins (ZFPs) that are used to construct them. While designed three-finger ZFNs may be sufficient to achieve targeted genome engineering of plants and animal cells in most cases, optimized four-finger ZFNs with higher sequence specificity and affinity would likely yield even better results. Optimized four-finger proteins appear to have both higher rates of targeting and less cytotoxicity in mammalian cells.

There is also excitement in the scientific community that ZFN-based strategies will make targeted correction of a genetic defect feasible in the future, especially in treating monogenic diseases. Several areas of research appear to be converging and coalescing to make gene therapy a reality. The complete nucleotide sequence of the human genome is now available. Also, rapid progress is being made in stem cell research. The first applications of ZFN-based strategies as a form of gene therapy to treat human diseases

will likely occur in *ex-vivo* gene therapy using stem cells. It must be emphasized that ZFN-based strategies as a form of gene therapy is still at its infancy. Several issues, like efficient gene delivery into the targeted cells and immune response to ZFNs, etc. still remain that need to be addressed very systematically and carefully before ZFNs can be considered for human therapeutics. Since the ZFNs will only be expressed transiently, it decreases the probability that they will invoke an undesired immune response but this remains to be tested. We expect that custom-designed ZFNs, the new type of molecular scissors that are engineered to target a unique site within the human genome, will contribute and greatly aid the feasibility of targeted and site-specific engineering of the human genome in the future. Ethical issues aside, we anticipate that over the next decade or so the technical problems associated with gene delivery will be overcome and that gene therapy will be routinely used in a clinical setting. This will finally signify a paradigm shift in the treatment of human diseases.