CRISPR/Cas9: Prospects and Challenges

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All science takes inspiration from nature, but nowhere is this more true than in biology, where some of the most powerful tools available to researchers are derived from natural products. From restriction enzymes and fluorescent proteins to microbial opsins and viral gene delivery vectors, researchers have capitalized on processes that occur in a variety of microbial, plant, and animal species. The recent development of the clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9 system for genome editing is yet another example of how scientists have learned from and adapted nature's inventions. The success of CRISPR/Cas9 also highlights another general tenet of science: basic, fundamental research can lead to transformative discoveries.

Originally, CRISPR/Cas9, a bacterial defense system, was studied by microbiologists aiming to understand bacterial immunity. In the past 5 years, however, attention shifted to developing CRISPR/Cas9 as a powerful tool for biological research. Harnessing the CRISPR/Cas9 system for genome editing and manipulation has accelerated research and expanded researchers' ability to generate genetic models. Whereas genetic manipulation had been largely limited to mice and rats, this new technology, with its ease of customization and high efficiency, has made it possible to manipulate virtually any model organism of choice. As a result, researchers are now empowered to generate models that best capture the needs of the scientific inquiry or most closely recapitulate specific disease biology. In addition, these new capabilities have drastically simplified genome editing in human cell lines, which has made possible direct testing of causal genetic variations linked to human diseases.

Further advances of the CRISPR/Cas9 toolbox are helping researchers discover new gene functions with high sensitivity and precision. For example, using the CRISPR/Cas9 system with tens of thousands of guides that are designed to target all coding genes in the human genome allows researchers to conduct genome-scale gain- and loss-of-function genetic screens. By quickly scanning through all of the genes in the genome, new gene candidates from a variety of assays ranging from cancer drug resistance to neurodegeneration will inform new strategies for combating diseases. Similarly, these comprehensive genetic screens may also identify novel disease-protective mutations such as the loss-of-function mutations in CCR5 and PCSK9, which result in protection against HIV infection and hypercholesterolemia, respectively.

In the future, another tantalizing application of the CRISPR/Cas9 technology is the direct treatment of deleterious genetic diseases through genome editing of somatic cells. By correcting disease-causing mutations, it may be possible to reverse disease symptoms. However, in order to optimize therapeutic potential, the appropriate delivery, specificity, and repair strategies must be established. Treatment of eye and hearing disorders using CRISPR/Cas9 are being actively evaluated in animal models, and more compact CRISPR/Cas9 components have been identified that allow the system to be delivered as a single unit. While some disorders may be treated through the correction of a small number of cells, the majority of genetic diseases may require the correction of a large number of cells in the affected tissue. On the horizon are improvements in homology-directed re-

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pair for use in non- or slowly-dividing cells. Given the potential benefit of genome editing-based therapies, many groups are now striving to make CRISPR/Cas9-based therapies a reality.

The exciting development of the CRISPR/Cas9 technology for genome editing also raises certain societal challenges and brings a sense of uncertainty and fear of catastrophic misuse. However, one thing is certain—nature will never cease to inspire us with its biological toolbox. We are compelled as scientists to explore the frontiers of the natural world and to seek out the mechanisms underlying it, some of which, like CRISPR/Cas9, may turn out to be the tools we use for future explorations. The tools themselves do not pose a threat, and it is my hope that the CRISPR/Cas9 technology will live up to its promise by being used responsibly and carefully.