

The therapeutic potential of phiC31 integrase as a gene therapy system.

Journal:	Expert Opin Biol Ther
Publication Year:	2011
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PubMed link:	21736536
Funding Grants:	Safe, efficient creation of human induced pluripotent stem cells without the use of retroviruses, Stem Cell Therapy for Duchenne Muscular Dystrophy, Site-specific integration of Lmx1a, FoxA2, & Otx2 to optimize dopaminergic differentiation

Public Summary:

This review article discusses recent progress, during the past 12 - 18 months, with the phiC31 integrase system. This is a system for adding genes to a cell. The system does not use a virus for gene addition. It uses an enzyme from a simple organism. This enzyme also works in cells from mammals, such as mice and humans. The enzyme places the introduced genes into a limited number of places in the chromosome. This is safer than placing genes into the chromosomes at random, which is what most viruses do. This integrase system has been widely used in gene therapy studies, where a therapeutic gene is added to cells or to a living animal. The most intense progress recently has been with use of the system in the liver, to treat hemophilia. The system has been shown to cure hemophilia in mice, but use in humans awaits the development of methods to deliver the DNA efficiently into the human liver. The most promising new use of the phiC31 integrase system is in stem cells. It has been used in a variety of adult human and animal stem cells. Even more promising is use of the system in pluripotent stem cells, such as embryonic stem cells and induced pluripotent stem (iPS) cells. It has been shown that the integrase system can be used to create iPS cells out of ordinary adult cells, through the addition of "reprogramming" genes that dial the cells back to a primitive state. In fact, the phiC31 integrase system possesses an outstanding fit for use in pluripotent stem cells, since delivery of DNA in cultured cells overcomes the inefficiency of DNA delivery to the body. Furthermore, since pluripotent stem cells can divide over and over again in culture, it is possible to work with a clone of cells that all have the same, safe integration site. The ease and efficiency of making and modifying iPS cells with phiC31 and other phage integrases suggests that this will become an important application of the phiC31 integrase system in the future.

Scientific Abstract:

INTRODUCTION: The phiC31 integrase system is a phage-derived system that offers the ability to integrate plasmid DNA into the chromosomes at a subset of endogenous preferred locations associated with robust gene expression. Recent progress highlights the unique advantages of this system for in vivo gene therapy and for use in stem cells. **AREAS COVERED:** The phiC31 integrase system has been under development for ten years and has been demonstrated to be effective for integration of plasmids in a variety of tissues and organs for gene therapy in animal systems, as well as in isolated human cells. We focus on work with the phiC31 integrase system during the past 12 - 18 months. This work has centered on a series of papers involving in vivo delivery of the integrase system to the liver and a variety of studies demonstrating the utility of the integrase system in stem cells. **EXPERT OPINION:** We conclude that the phiC31 integrase system has significant potential for liver gene therapy, if effective DNA delivery methods for large mammals become available. The phiC31 integrase system displays an outstanding fit for use in pluripotent stem cells, and this area is expected to be the subject of intense development.