Gene Therapy Approaches to Human Immunodeficiency Virus and Other Infectious Diseases

Geoffrey L. Rogers, PhD, Paula M. Cannon, PhD*

KEYWORDS

• Gene therapy • HIV • Gene editing • Targeted nuclease • Cas9 • AAV

KEY POINTS

- Recent innovations and clinical successes in gene therapy have provided the impetus to apply these techniques toward the treatment of infectious diseases, particularly human immunodeficiency virus (HIV).
- One significant gene therapy for HIV currently in translation involves the use of zinc finger nucleases to disrupt the HIV coreceptor CCR5, rendering T cells resistant to HIV infection.
- Targeted nucleases are being developed to disrupt or excise proviral DNA in HIV and hepatitis B virus infection, directly targeting latent viral reservoirs that are invisible to the immune system.
- Gene transfer using adeno-associated virus vectors allows systemic expression of broadly neutralizing antibodies against HIV, influenza, and respiratory syncytial virus, representing an approach for long-lived passive immunization.
- Gene therapy also allows for combinatorial approaches, targeting multiple aspects of a pathogen, and potentially paving the path toward long-term suppression or cure for HIV and other pernicious infections.

INTRODUCTION

Gene therapy has experienced a significant revival in recent years, with several successes in the treatment of monogenetic disorders[1] and cancer.[2] Gene therapy is now also being considered for serious infectious diseases, led by a focus on the human immunodeficiency virus (HIV). Although antiretroviral therapy (ART) can control

Disclosure Statement: The authors have nothing to disclose.
Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, 2011 Zonal Avenue, HMR 413A, Los Angeles, CA 90033, USA
* Corresponding author. Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, 2011 Zonal Avenue, HMR 413A, Los Angeles, CA 90033.
E-mail address: pcannon@usc.edu

Hematol Oncol Clin N Am 31 (2017) 883–895
http://dx.doi.org/10.1016/j.hoc.2017.06.008 **hemonc.theclinics.com**

HIV infection in most patients, there is currently no vaccine or cure for the virus due to its high mutagenic rate, subversion of the host immune system, and ability to remain latent for extended periods of time in long-lived T cells.[3,4] The lone exception to this stark reality is the so-called Berlin patient, who seems to have been cured of HIV following a bone marrow transplant from a donor with 2 copies of a defective CCR5 gene, CCR5Δ32, which is a commonly used coreceptor for HIV.[5] This case renewed excitement for the potential of gene therapy to be used against HIV and, in particular, by using the new tools available in the field.[6,7]

GENE EDITING: ENGINEERING RESISTANCE TO VIRUSES

In addition to classic gene therapies mediated by viral vectors, targeted nucleases such as the CRISPR/Cas9 system have sparked a revolution in gene therapy by making possible site-specific gene editing.[8] Although CRISPR/Cas9 is similar in action and efficacy to protein-based targeted nucleases, such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs),[9] the ease of design and testing of these reagents through the construction of single-guide RNAs (sgRNAs) has made gene editing available for a wider variety of users and applications.

Targeted nucleases can cut, nick, or bind DNA in a sequence-specific manner, and have thereby made possible several novel applications that were not previously feasible in humans.[10] One notable application of these reagents is to achieve permanent gene disruption. Following the creation of a double-stranded break (DSB) within the coding sequence of a gene, error-prone nonhomologous end-joining (NHEJ) DNA repair can result in insertions and deletions (indels) that result in frameshift or nonsense mutations that inactivate the gene. Much of the groundwork for using these types of strategies was developed or considered using therapeutic RNA interference (RNAi),[11–13] but nuclease-mediated gene disruption has the advantage of providing permanent and more complete gene knockdown, with the possibility of engineering long-lived resistance to pathogenic organisms.

In addition to the NHEJ repair pathway, DSBs can also be repaired by homology-directed repair (HDR) pathways.[14] By providing a DNA homology template along with a targeted nuclease, it is possible to exploit these pathways to either insert a gene into a specific site within the host DNA or to mutate a gene to create a more desirable variant.[10] The homology templates can be introduced using plasmids or single-stranded DNA oligonucleotides, but more success has been achieved in sensitive primary cells using viral vectors based on adeno-associated virus (AAV) or integrase-deficient lentivirus.[15–17]

These techniques, along with more classic gene therapy approaches using viral vectors to express genes or RNA regulators, provide a variety of approaches for the treatment of HIV and other infectious diseases. This article discusses several different gene therapy strategies that take advantage of these various platforms and approaches (**Fig. 1**).

ELIMINATING VIRAL ENTRY RECEPTORS

In the context of HIV infection, gene disruption technologies provide the potential to replicate the case of the Berlin patient, who received a CCR5Δ32 bone marrow transplant, by introducing CCR5 mutations into autologous lymphocytes or the precursor hematopoietic stem and progenitor cells (HSPCs).[18] The CCR5Δ32 mutation is relatively common in European populations and has not been associated with any major deleterious phenotype.[19] By packaging engineered ZFNs targeting CCR5 into