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# An invited review following *the Soujinkai Fujiu Memorial Award*: A Cure for Chronic Viral Infectious Diseases - Bridging Basic Science to Clinical Applications

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## Main Text

Obtaining a cure against an infectious disease involves eliminating the pathogenic microbe from the patient. In acute viral infections, such as influenza, the pathogen becomes undetectable as the patient recovers. After symptoms have disappeared, the patient becomes free of the viral pathogen, although this may take several weeks or even months. This is attributed to the power of immunity. By contrast, some viruses that establish latent or chronic infections are difficult ,if not impossible, to get rid of. These include human T-cell leukemia virus type I (HTLV-1) and human immunodeficiency virus (HIV), both of which belong to the human retrovirus family.[1,2] The retroviral genome is made up of RNA, which is converted to DNA when the virus enters the cell. Then, the viral genome is integrated into the chromosomal DNA as a provirus. Once integrated, the proviral DNA behaves like the host chromosomal DNA and cannot be distinguished easily from the cellular genome. Current medical technology is unable to remove the provirus from infected cells. Thus, at present, we cannot cure retroviral infections, which quite often persist

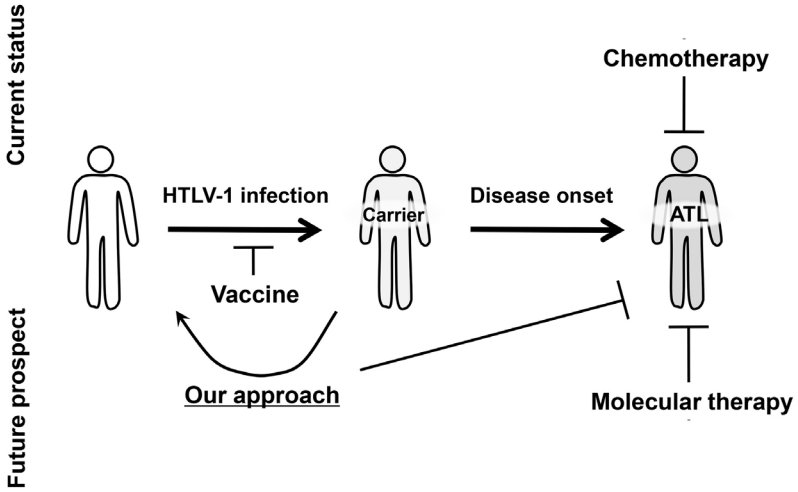


Fig. 1 Current status and future prospect of strategies toward HTLV-1 infection. No cure protocol is currently available for HTLV-1 infection. Our approach aims to cure HTLV-1 infection as well as to treat ATL by adopting a genome editing technique targeting the proviral DNA.

until the death of the patient (Fig. 1). Vaccines are excellent tools for preventing pathogen infections. Unfortunately, no vaccine is currently available to combat HTLV-1 or HIV infections.

HTLV-1 is a causative agent of adult T-cell leukemia (ATL) and myelopathy (HAM).[1] There is currently no medicine that is specifically effective against ATL or HAM. HIV-1 causes acquired immunodeficiency syndrome (AIDS).[2] By contrast to HTLV-1 infection, molecular medicines are available to slow down the disease progression of HIV-1 infection, but these medicines must be taken for the entire life of the patient and thus do not result in a cure.

We set out to develop a new approach to cure HTLV-1 infection. We used an artificial enzyme called Zinc Finger Nuclease (ZFN),[3] which introduces a double strand break (DSB) into DNA upon substrate recognition. We designed a pair of ZFN molecules that specifically recognizes the long terminal repeat (LTR) of HTLV-1 provirus. When they were transduced, the HTLV-1-infected cells underwent programmed cell death.[4] More importantly, we found that this molecular approach had the potential to remove the proviral DNA from the infected cells. This is the first report providing scientific evidence that obtaining a cure of HTLV-1 infection is feasible. The technology is still under laboratory development, and although it will need more time and effort to develop clinical applications based on this strategy, the work is notable because we expect it will have an important impact on the direction of future therapies designed to specifically target HTLV-1 infection. We believe that this proof-of-concept study finally offers HTLV-1-infected individuals a glimpse of a cure.

The scope of the above approach is not restricted to HTLV-1 infection, but could also serve as a basis for novel therapies against other chronic viral infections, including Epstein-Barr virus (EBV), which also causes malignant disorders.[5] We have reported and will continue to report new methodologies, based on molecular to population approaches, to combat both acute and chronic infectious diseases.[6-20] The methodologies we have developed reveal the Achilles' Heel of pathogen infection, which could serve as a platform for the development of novel therapies that target the underlying molecular determinants specific to each infectious disease. Our mission is to conduct basic science and bridge it to clinical applications against infectious diseases that still continue to threaten human health globally.

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## Conflict of Interest

The author states no conflict of interest.

## References

1. Fujii, M. and Matsuoka, M. : Human T-Cell Leukemia Virus Types 1 and 2. *In* Knipe D.M., Howley P.M. (ed.), *Fields Virology*, 6th Edition. Volume 2. Lippincott Williams & Wilkins, Philadelphia, PA, USA, 2013, pp. 1474-1501.
2. Kuritzkes, D.R. and Koup, R.A.: HIV-1: Pathogenesis, Clinical Manifestations, and Treatment. *In* Knipe D.M., Howley P.M. (ed.), *Fields Virology*, 6th Edition. Volume 2. Lippincott Williams & Wilkins, Philadelphia, PA, USA, 2013, pp. 1561-1583.
3. Jacob, H.J., Lazar, J., Dwinell, M.R., Moreno, C. and Geurts, A.M.: Gene targeting in the rat: advances and opportunities. *Trends genet.*, **26**(12): 510-518, 2010.
4. Tanaka, A., Takeda, S., Kariya, R., Matsuda, K., Urano, E., Okada, S., et al.: A novel therapeutic molecule against HTLV-1 infection targeting provirus. *Leukemia*, **27**(8): 1621-1627, 2013.
5. Longnecker, R.M., Kieff, E. and Cohen, J.I.: Epstein-Barr Virus. *In* Knipe D.M., Howley P.M. (ed.), *Fields Virology*, 6th Edition. Volume 2. Volume 2. Lippincott Williams & Wilkins, Philadelphia, PA, USA, 2013, pp. 1598-1959.
6. Komano, J., Miyauchi, K., Matsuda, Z., and

Yamamoto, N.: Inhibiting the Arp2/3 complex limits infection of both intracellular mature vaccinia virus and primate lentiviruses. *Mol. Biol. Cell.*, **15**(12): 5197-5207, 2004.
7. Shimizu, S., Urano, E., Futahashi, Y., Miyauchi, K., Isogai, M., Matsuda, Z., et al.: Inhibiting lentiviral replication by HEXIM1, a cellular negative regulator of the CDK9/cyclin T complex. *AIDS*, **21**(5): 575-582, 2007.
8. Fuji, H., Urano, E., Futahashi, Y., Hamatake, M., Tatsumi, J., Hoshino, T., et al.: Derivatives of 5-nitro-furan-2-carboxylic acid carbamoylmethyl ester inhibit RNase H activity associated with HIV-1 reverse transcriptase. *J. Med. Chem.*, **52**(5): 1380-1387, 2009.
9. Urano, E., Kuramochi, N., Ichikawa, R., Murayama, S.Y., Miyauchi, K., Tomoda, H., et al.: Novel postentry inhibitor of human immunodeficiency virus type 1 replication screened by yeast membrane-associated two-hybrid system. *Antimicrob. Agents Chemother.*, **55**(9): 4251-4260, 2011.
10. Saitoh, T., Komano, J., Saitoh, Y., Misawa, T., Takahama, M., Kozaki, T., et al.: Neutrophil extracellular traps mediate a host defense response to human immunodeficiency virus-1. *Cell Host Microbe*, **12**(1): 109-116, 2012.
11. Zhang, X., Sobue, T., Isshiki, M., Makino, S., Inoue, M., Kato, K., et al.: Elicitation of both anti HIV-1 Env humoral and cellular immunities by replicating vaccinia prime Sendai virus boost regimen and boosting by CD40Lm. *PloS ONE*, **7**(12): e51633, 2012.
12. Miyauchi, K., Urano, E., Takizawa, M., Ichikawa, R., and Komano, J.: Therapeutic potential of HIV protease-activable CASP3. *Sci. Rep.*, **2**: 359, 2012.
13. Hashimoto, C., Nomura, W., Ohya, A., Urano, E., Miyauchi, K., Narumi, T., et al.: Evaluation of a synthetic C34 trimer of HIV-1 gp41 as AIDS vaccines. *Bioorg. Med. Chem.*, **20**(10): 3287-3291, 2012.
14. Lee, H., Komano, J., Saitoh, Y., Yamaoka, S., Kozaki, T., Misawa, T., et al.: Zinc-finger antiviral protein mediates retinoic acid inducible gene I-like receptor-independent antiviral response to murine leukemia virus. *Pro. Natl. Acad. Sci. U. S. A.*, **110**(30): 12379-12384, 2013.
15. Urano, E., Morikawa, Y., and Komano, J.: Novel role of HSP40/DNAJ in the regulation of HIV-1 replication. *J. Acquir. Immune Defic. Syndr.*, **64**(2): 154-62, 2013.
16. Kurata, T., Kanbayashi, D., Kinoshita, H., Arai, S., Matsui, Y., Fukumura, K., et al.: Late onset of vaccine-associated measles in an adult with severe clinical symptoms: a case report. *Am. J. Med.*, **127**(4): e3-4, 2014.
17. Kojima, Y., Kawahata, T., Mori, H., Furubayashi, K., Taniguchi, Y., Itoda, I., et al.: Identification of Novel Recombinant Forms of Hepatitis B Virus Generated from Genotypes Ae and G in HIV-1-Positive Japanese Men Who Have Sex with Men. *AIDS Res. Hum. Retroviruses*, **31**(7): 760-767, 2015.
18. Kurata, T., Kanbayashi, D., Nishimura, H., Komano, J., Kase, T., and Takahashi, K.: Increased reports of measles in a low endemic region during a rubella outbreak in adult populations. *Am. J. Infect. Control*, **43**(6): 653-655, 2015.
19. Sakon, N., Yamazaki, K., Nakata, K., Kanbayashi, D., Yoda, T., Mantani, M., et al.: Impact of genotype-specific herd immunity on the circulatory dynamism of norovirus: a 10-year longitudinal study of viral acute gastroenteritis. *J. Infect. Dis.*, **211**(6): 879-888, 2015.
20. Mori, H., Kojima, Y., Kawahata, T., Matsuura, M., Uno, K., Konishi, M., et al.: A cluster of rapid disease progressors upon primary HIV-1 infection shared a novel variant with mutations in the p6gag/pol and pol/vif genes. *AIDS*, **29**(13): 1717-1719, 2015.