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Editorial overview: Engineering cellular resistance towards the HIV cure

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HIV is one of the few retroviruses that can transmit between individuals and cause human disease. Unfortunately, the persistent infection that is caused by HIV triggers — after several years — a deadly disease: the acquired immunodeficiency syndrome (AIDS). HIV infects CD4-positive immune cells, leading to a reduction in their number and consequently a damaged immune system, allowing opportunistic infections and cancers to pop up. Without treatment, HIV-infected individuals eventually die. Without prevention and intervention measures, in some countries nearly 40% of the population has been infected by HIV in the past. From a few dozens of reported AIDS cases in 1981, in less than 10 years, HIV infections reached more than 10 million by 1990. The devastating impact of HIV on the entire society, the grave challenges to treat HIV infection, and the decades long intense battle against a single viral pathogen have been unprecedented.

Undeniably, we have made extraordinary progress in the fight against HIV/AIDS, but we have not won the battle yet. The most effective and impactful intervention that we have generated is arguably the antiretroviral therapy, starting with AZT, the first reverse transcriptase (RT) inhibitor that was approved by the FDA for clinical use in 1987. However, it took many more years to impose the first decline in the number of HIV-related deaths. Key was the development of a new class of anti-HIV drugs in 1995: HIV protease inhibitors that could be used in combination with RT inhibitors. Today, we have more than 30 HIV inhibitors from several drug classes and combined antiretroviral therapy (cART) is able to persistently suppress the viral load in patients. This has transformed HIV infection from a deadly disease to a chronic, manageable medical condition. The battle against HIV has been a hard one with the sad loss of 35 million infected patients, but the lives of some 37 million living with HIV could be saved due to access to cART. However, cART has to be continued life long and may cause side effects. Above all, HIV infection can still not be cured.

But the dawn may be at the horizon. This issue of *Current Opinion in Virology* presents ten insightful reviews highlighting several major lines of progress in the quest for an HIV cure, illuminating the possible future directions we may take, and discussing the powerful new tools that we may employ to develop the HIV cure.

As was noticed early on in the HIV epidemic, there is much patient-to-patient variation in the course of disease. For instance, nature presented cases in which individuals were repeatedly exposed to HIV, but never got infected, the so-called highly exposed seronegative individuals. Some

people can get infected, but are able to suppress the virus below a certain threshold and do not progress to AIDS, the elite controllers. Hopefully, if we understand how these special groups manage to fend off HIV infection, we may be able to apply this knowledge to help other HIV patients to contain HIV and to achieve a functional cure. Cecilio Lopez-Galindez *et al.* (Instituto de Salud Carlos III, Spain) elegantly reviewed the host cell and viral factors that together may have enabled the elite controllers to survive HIV infection. It is apparent that these individuals have benefited from unique combinations of host factors to restrict HIV replication.

Despite many years of hard work by numerous researchers, we still have limited knowledge of the actual composition of the HIV reservoir, which is a poor starting position for any therapeutic attempt to target and eliminate these reservoir cells. A major challenge is to identify the different cell types and organs that contribute to this HIV reservoir. Chris Power *et al.* (University of Alberta, Canada) discussed the nature of HIV reservoir cells in the brain and the potential strategies to eradicate HIV reservoirs in this special anatomic site.

The barrier to eliminate HIV from a patient is the latent HIV reservoir. This viral reservoir is established in the early stage of infection and lasts for decades, even in the presence of cART. These HIV reservoir cells often carry transcriptionally dormant viral DNA that is integrated in the host cell DNA. As these cells do not express viral proteins, they are not seen by the host immune system. Carine van Lint *et al.* (Université Libre de Bruxelles, Belgium) discussed research aimed at deciphering the molecular mechanisms of HIV persistence.

While striving to understand the true nature and the detailed anatomic locations of HIV reservoirs, a variety of strategies have already been put forward for curing HIV infection. The foremost approach is 'shock and kill', which is based on the concept that the immune system is able to detect and clear the reservoir cells if the latent HIV DNA is activated by select agents to express viral antigens. Sharon Levin *et al.* (University of Melbourne, Australia) presented an update on this endeavor, recapping the lessons from several recent clinical trials, and raising hope for this strategy in light of the promising results obtained with new shock agents like TLR7 agonists. Takomeh Mahmoudi *et al.* (Erasmus University Medical Center, the Netherlands) provided a concise and comprehensive overview of latency reversal agents, HIV-blocking agents, and drugs that induce cell death, thereby assisting in clearance of the HIV-infected cells.

In addition to discovering agents that are able to activate and purge the heterogeneous HIV reservoir cells, success of the 'shock and kill' strategy also depends on efficient killing of the activated reservoirs. Unfortunately, HIV infects and kills CD4+ immune cells, and wrecks the immune system. Even with long-term and powerful cART, the function of the host immune system is hardly restored to the normal level, which inevitably undermines the efficacy of a 'shock and kill' strategy. To compensate for deficient immunity, different types of immunotherapy have been designed and tested to assist in the killing of HIV-infected cells. Hui Zhang *et al.* (Sun Yat-sen University, China) reviewed one such strategy, the CAR-T technology. The concept is to engineer T cells that can recognize the HIV envelope protein in order to kill HIV-infected cells. It is hoped that CAR-T will boost the efficacy of 'shock and kill' strategies in clearing the HIV reservoir.

Another immunological avenue to reduce and even to clear HIV reservoirs is the employment of broadly neutralizing antibodies (bnAbs). This special class of Abs can be found in about 10% of chronically infected HIV patients. Since their first isolation and characterization, more than a dozen bnAbs have been identified that target conserved epitopes on the HIV gp120/gp41 envelope protein. In addition to guiding the development of vaccine immunogens that are expected to elicit protection against a broad range of circulating HIV strains, bnAbs have also been pursued as new therapeutics. Marit van Gils *et al.* (University Medical Centers Amsterdam, the Netherlands) highlighted the advantages of bnAbs-based therapy over cART, stressing the potential of bnAbs in efforts to diminish and hopefully eliminate the HIV reservoirs

A converse and equally promising HIV cure strategy is 'block and lock'. The underlying principle is to permanently halt HIV gene expression and lock HIV in its latent state, thus attaining a functional cure of the HIV infection. Andrew Henderson *et al.* (Boston University School of Medicine, USA) reviewed the mechanism of HIV proviral transcription, its contribution to HIV latency and the design of repressors of HIV transcription as a 'block and lock' cure strategy.

Inspired by the cure of the 'Berlin patient' and the recent 'London patient', efforts have been made to modify hematopoietic stem cells to make them resistant to HIV infection through strategies including mutation of the CCR5 gene that encodes the critical co-receptor for HIV-infection. Anne Gatignol *et al.* (Lady Davis Institute for Medical Research, Canada) reviewed approaches to produce HIV-resistant cells by the expression of small RNA molecules, including short hairpin RNAs that trigger the RNA interference mechanism, RNA decoys and aptamers that bind and inactivate an HIV protein or transcript, and ribozymes that mediate cleavage of viral transcripts.

One genuine marker that distinguishes latent HIV reservoir cells from the neighboring uninfected cells is the presence of the integrated HIV DNA (the provirus) that is randomly integrated on one of the chromosomes of the host cell. As said, cells with a silent/latent provirus will survive preferentially due to immune escape. Elimination of this latent HIV DNA equates curing of HIV-infected cells. This ultimate goal has been pursued with different gene editing tools, ranging from zinc finger nucleases, transcription activator-like effector nucleases and recombinases to the most recent CRISPR technology. Atze Das *et al.* (University of Amsterdam, the Netherlands) reviewed the progress that has been made in overcoming HIV resistance to CRISPR editing. In particular, promising results are presented concerning a sterilizing cure of HIV-infected cells in tissue culture by a combinatorial CRISPR treatment..

After having presented multiple lines of attack on the HIV reservoir, which of these avenues will succeed in achieving the HIV cure? We cannot predict this and success may depend on a combination of approaches. Breakthroughs can also come from other surprise directions, which is the true nature of research. It would thus seem important to fill the cure pipeline with a diversity of sometimes unorthodox approaches to increase the chances of eventual success. But we do know that further knowledge of the actual HIV reservoirs, including their heterogeneous nature and clonal properties, will be important baseline information. We all realize that the medical urgency of HIV epidemic continues and that development of a safe HIV cure will relieve millions of HIV-infected individuals from daily medication..