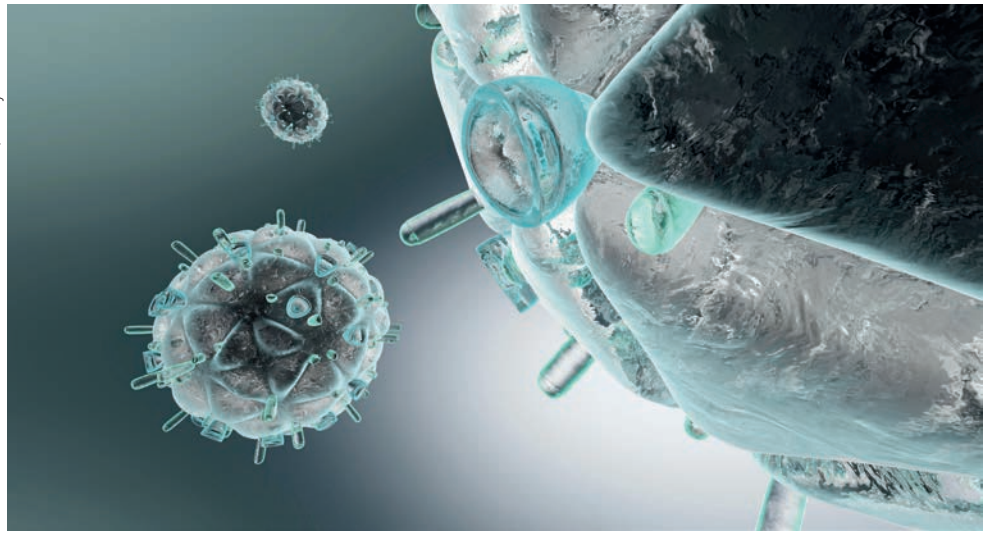

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MILESTONE 3

CD4 opens the door

Like an uninvited visitor tricking the host to gain entry, viruses induce 'door-opening' cellular processes like endocytosis by engaging the host cell's surface proteins. Although not intended by the host cell to function as viral entry receptors, these proteins are subverted into a gateway role by the virus.

CD4 was originally described in 1979 by Ellis Reinherz in Stuart Schlossman's lab as helper T lymphocyte antigen. Four years later, Luc Montagnier's group reported that HIV-1 was contained within the CD4$^+$ T cell fraction isolated from a patient with HIV-1 and selectively infected and depleted CD4$^+$ T cells in healthy-donor-derived lymphocyte cultures. The authors postulated HIV-1 tropism for CD4$^+$ T cells and speculated that the virus mediates CD4$^+$ T cell loss in AIDS. They also noted normal CD4$^+$ T cell numbers in one HIV-1-positive individual, raising the question of what factors constitute the in vivo determinants of HIV-1cytopathology, a puzzle that took decades to solve.

In 1984, two seminal studies showed that CD4 is critical for HIV-1 entry. In the absence of HIV-1-specific reagents, Robin Weiss and colleagues postulated CD4's role as an HIV-1 receptor using two proxy readouts of HIV-1 entry: multinucleated syncytia formation and cell lysis by vesicular stomatitis virus (VSV) virions bearing HIV-1 envelope proteins. This approach was a fortuitous choice, as native HIV-1 entry requires co-receptors unknown at that time (MILESTONE 15). CD4-specific antibodies blocked HIV-1-induced syncytia formation in cell lines. In parallel, Montagnier's team reported that anti-CD4 antibodies blocked HIV-1 replication in primary T cells. The *CD4* gene was cloned in 1985 by Richard Axel and colleagues, who then introduced recombinant *CD4* cDNA into HIV-1-resistant CD4-negative cells, conferring susceptibility to virus infection. Together with later characterization of CD4 binding to the HIV-1 envelope glycoprotein gp120, this research led the way to the development of HIV-1 entry-targeting therapies, elucidation of CD4's role in HIV-1 pathogenesis and characterization of HIV-1 cellular reservoirs.

In the clinic, CD4$^+$ T cell depletion was recognized as a hallmark of AIDS from the outset (MILESTONE 13), and a CD4$^+$ T cell count of less than 200 cells per microliter of blood is now part of the defining features of AIDS. Although HIV-1 seropositivity was instrumental in determining HIV-1 status, CD4$^+$ T cell count remained unrivalled as a quantitative measure of pathology in the era preceding tests for viral RNA load. During that time, CD4$^+$ T cell count was the key prognostic factor for immune function loss and an essential biomarker of therapeutic efficacy. To this day, CD4$^+$ T cell count informs disease staging and therapeutic choices.

> “CD4 is critical for HIV-1 entry”

Yet, reliance on CD4 for clinical decisions historically had drawbacks. Until blood immunophenotyping standardization in the 1990s, results varied considerably across medical centers. Along with natural variation in CD4$^+$ T cell counts across individuals and age groups, this contributed to diagnostic inconsistencies. Moreover, the decade-long lag between HIV-1 acquisition and the decline to very low levels of CD4$^+$ T cells in blood posed another major challenge to understanding AIDS epidemiology and the link to HIV-1. Finally, antiretroviral therapy was initially indicated only once blood CD4$^+$ T cell counts declined, as the virus was considered dormant until then (MILESTONE 16, 21).

This view was overturned by reports of acute CD4$^+$ T cell depletion in the gut. In fact, activated memory CD4$^+$ T cells, which are particularly permissive to HIV-1 replication and abundant in the intestine, are destroyed within days of infection in all tissues and in the circulation (MILESTONE 11). Loss of memory CD4$^+$ T cells impairs replenishment of the mature T cell pool, thus contributing to systemic CD4$^+$ T cell depletion (MILESTONE 13).

These studies illustrate the importance of research into viral entry receptors. CD4 opens the door to HIV-1, but it has also unlocked insights leading to disease control and prevention (MILESTONE 9, 20, 21).

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ORIGINAL ARTICLES Klatzmann, D. et al. Selective tropism of lymphadenopathy associated virus (LAV) for helper-inducer T lymphocytes. *Science* **225**, 59–63 (1984) | Dalgleish, A. G. et al. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. *Nature* **312**, 763–767 (1984) | Klatzmann, D. et al. T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. *Nature* **312**, 767–768 (1984) | Maddon, P. J. et al. The T4 gene encodes the AIDS virus receptor and is expressed in the immune system and the brain. *Cell* **47**, 333–348 (1986) | Veazey, R. S. et al. Gastrointestinal tract as a major site of CD4$^+$ T cell depletion and viral replication in SIV infection. *Science* **280**, 427–431 (1998) | Smit-McBride, Z., Mattapallil, J. J., McChesney, M., Ferrick, D. & Dandekar, S. Gastrointestinal T lymphocytes retain high potential for cytokine responses but have severe CD4$^+$ T-cell depletion at all stages of simian immunodeficiency virus infection compared to peripheral lymphocytes. *J. Virol.* **72**, 6646–6656 (1998) | Mattapallil, J. J. et al. Massive infection and loss of memory CD4$^+$ T cells in multiple tissues during acute SIV infection. *Nature* **434**, 1093–1097 (2005)