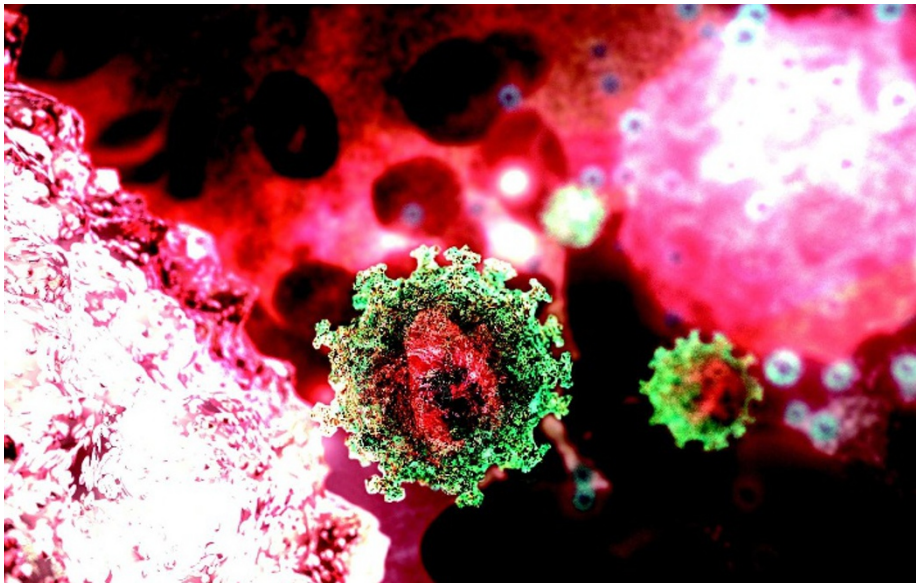
COMMENTARY

HIV immunology needs a new direction

Researchers need to get past the standard model of vaccine development and focus on how immune responses are specifically tailored to retroviruses, argue **Ruslan Medzhitov** and **Dan Littman**.



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Understanding how cells initially sense and recognize HIV could aid vaccine development (computer art).

Recent advances in immunology and failures in HIV-vaccine development suggest that it is time to rethink the current approach to developing an HIV vaccine. Better communication and cooperation is needed between vaccinologists, virologists and the growing number of researchers studying innate immune responses. HIV has evaded the attempts of vaccinologists for 25 years partly because of the unique characteristics of the virus, including its extremely high mutation rate, which enables immune evasion, and its ability to infect and deplete the major orchestrators of the immune response — the $CD4^+$ T cells. But, in our opinion, there are other reasons for failure.

Although vaccination arguably represents biomedical science's greatest triumph over disease, so far the successes can largely be ascribed to empirical findings, scattershot approaches that have yielded great dividends for scourges such as smallpox and polio, but little to speak of for others including HIV and malaria. This reflects our current, clearly limited, level of understanding of the immune system. Specifically, the 'rules' for making a successful vaccine are currently unknown.

If there is any guiding principle to this formidable task, it is that a vaccine should mimic, as much as possible, the immune recognition events that happen during a natural infection with the same pathogen. These would be likely to engage the appropriate mechanisms of immune protection. This is why attenuated pathogens are the most successful vaccines currently available. For HIV, the use of attenuated strains is not an option at present. We therefore need to understand how the virus is normally sensed by the immune system.

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Our understanding of early host responses, although incomplete, has improved dramatically in the past decade owing to a focus on the innate immune system, a first responder to pathogens that induces antimicrobial defence mechanisms and activates adaptive immunity. The human immune system has to deal with a variety of pathogens, ranging from RNA viruses to 30-foot-long tapeworms. Naturally, the ways in which these intruders are sensed and handled vary. Indeed several families of microbial sensors have now been identified that detect different classes of pathogens and trigger activation of adaptive immunity by different mechanisms[1,2].

Major gaps remain in the understanding of how HIV and retroviral infection in general is sensed by the innate immune system, and how this initial sensing is translated into the activation of adaptive immunity. In our view, there is currently insufficient effort being devoted to addressing these gaps and this is irreconcilable with the urgent need for a vaccine.

Studying HIV is of course complicated by its human-specific tropism, which precludes many definitive experiments. Although the mouse, as a model system, is often dismissed as irrelevant to HIV infection, there are likely to be common basic principles of retroviral immune recognition that need to be defined. Innate sensors may recognize features of replication that are shared among retroviruses but no other classes of viruses. For example, newly reverse-transcribed retroviral DNA may activate a specialized signalling pathway. Further study of the numerous host factors co-opted by HIV for its replication[3] might provide insight, as these may recruit antiviral innate sensors that limit viral spread.

Approaches currently used in HIV vaccine development are largely based on immunological paradigms wrought from studies using antigen immunizations and infections with several model pathogens. These paradigms may not apply to retroviral infections. In the absence of a basic understanding of how the host immune system responds to retroviral infection, the approaches tried so far have been more or less random, and unsuccessful, attempts to see what might work. Most of the resources devoted to HIV vaccine development have been spent on such efforts, which may remain futile until we gain some understanding of the basic mechanisms of retroviral recognition and induction of adaptive immune responses. ■

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