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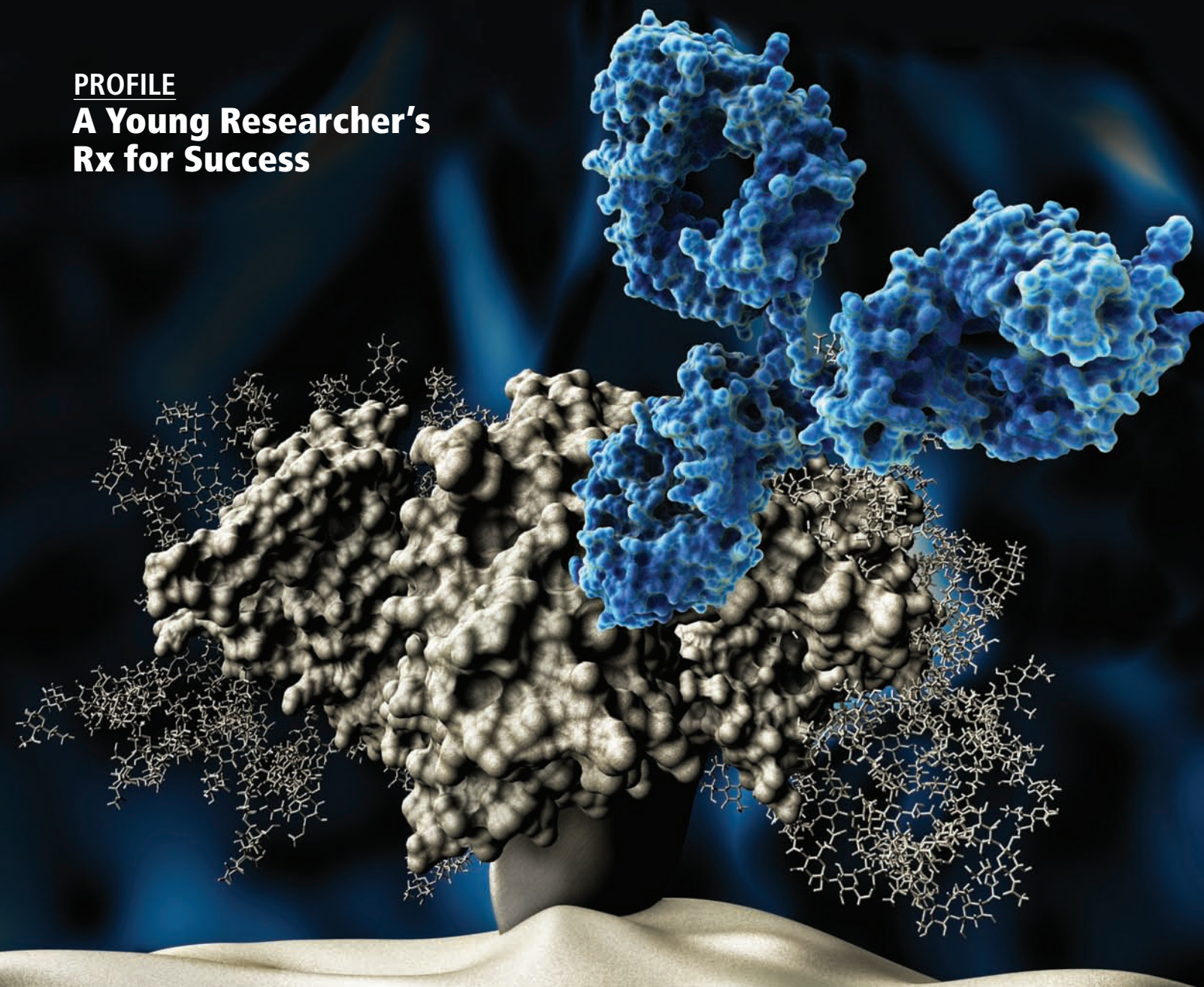
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AIDS VACCINE 2010

ADVANCES ABOUND

PROFILE

**A Young Researcher's
Rx for Success**



Research BRIEFS

Clues Found About How HIV-1 Avoids Triggering Innate Immune Responses

THE INNATE IMMUNE RESPONSE is activated within hours after direct recognition of pathogens. This first-line response helps to contain the pathogens and present them to the adaptive immune system. Many bacteria and viruses can induce innate immune responses, but there is not much evidence for direct innate immune responses to retroviruses, including HIV-1, perhaps at least in part because HIV-1 has evolved elaborate strategies to evade triggering innate immunity.

Just how HIV-1 evades triggering innate immune responses is now becoming clearer from two recent studies in which researchers were able to trick HIV-1 to induce innate immune responses in cells in which it does not normally induce such responses. Dan Littman, an investigator at the Howard Hughes Medical Institute at the Skirball Institute at New York University School of Medicine, and colleagues reported that they were able to induce an innate immune response to HIV-1 in dendritic cells (DCs; *Nature* 467, 214, 2010), and Judy Lieberman, a professor of pediatrics at Harvard Medical School, and colleagues showed the induction of an innate immune response to HIV-1 in CD4⁺ T cells and macrophages (*Nat. Immunol.* 11, 1005, 2010).

The two groups used different methods to trigger an innate immune response to HIV-1 in these different cell types. Because DCs mostly resist productive infection with HIV-1, Littman and colleagues used a previously developed strategy to overcome this resistance by delivering HIV-1 to DCs together with simian immunodeficiency virus (SIV) virus-like particles that carry a protein called Vpx (*Gene Ther.* 13, 991, 2006). This strategy is based on the finding that in DCs, the viral replication cycle of HIV-1 is blocked at several points, whereas SIV and HIV-2 have a protein called Vpx

that can counteract one of these blocks.

When Littman and colleagues used this strategy to productively infect DCs with HIV-1, they found, to Littman's surprise, that the infected DCs produced type I interferon (IFN), a strong inhibitor of viral replication and a sign that the DCs had recognized HIV-1 as dangerous and activated an innate immune response against it.

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— Dan Littman

Lieberman and colleagues induced a direct innate immune response and IFN production in HIV-1 infected CD4⁺ T cells and macrophages by inhibiting the expression of a human host cell protein called TREX1, which normally degrades cytoplasmic HIV-1 DNA in the infected cell. This suggests that in CD4⁺ T cells and macrophages TREX1 helps HIV-1 avoid inducing an innate immune response in infected CD4⁺ T cells by degrading HIV-1 DNA.

"I think the key point of both studies is that HIV evades triggering innate immunity either by not efficiently infecting dendritic cells, [or] in our case [by getting help from a host gene] we need to knock down to get IFN induction," says Lieberman.

In addition, Littman says the induction of an innate immune response in DCs suggests that it should be possible, in principle, to develop improved HIV-1 vaccine candidates that can induce an innate immune response in DCs. "[This study] finally opens the door to studying direct innate responses to HIV infection in the host, something that has just not been really observed prior to this in a way that could be significant for controlling the virus," he says. "The most interesting implication would be that it may be possible to develop vaccines that specifically target DCs to improve the activation of T cells specific against the virus." Lieberman agrees but adds that "most vaccines that use live vectors or adjuvants should activate innate immunity, which enhances the adaptive immune response."

The TREX1 finding might also be applicable to vaccine development, Lieberman says. "Inhibiting TREX1, which degrades cytoplasmic DNA, might enhance immunity to DNA vaccines possibly by having them trigger innate immunity," she says. "In my opinion one reason they are not that potent is that they don't provide a danger signal."

One reason elite controllers can control HIV-1 infection without treatment could be that somehow these individuals can activate an innate immune response against the virus. "Maybe there is some genetic predisposition in those elite controllers that allows either the virus to gain access to DCs or allows the T cells to mount a type I IFN response following infection," Littman says. "It would be worth exploring whether exposed but uninfected individuals or elite controllers might have differences in some of the genes involved, such as in *TREX1*," adds Lieberman. —*Andreas von Bubnoff*