AIDS researchers have long known that HIV cannot copy itself in monkeys, but they had only a vague idea why. Now, a critical piece of this puzzle has fallen into place: Monkey cells make a protein that specifically details HIV. Aside from helping solve a long-standing mystery, the finding may lead to new strategies for drugmakers, as well as an improved monkey model to test anti-HIV drugs and vaccines.

Researchers led by virologist Joseph Sodroski of the Dana-Farber Cancer Institute in Boston report in the 26 February issue of *Nature* that they fished a protein from monkey cells, TRIM5-α, that powerfully restricts HIV's ability to establish an infection. Although HIV can easily enter monkey cells, the virus must convert its RNA into DNA before it can weave itself into the host's chromosomes and copy itself. TRIM5-α blocks the transcription of RNA into DNA, the same part of the viral life cycle that AZT and several other anti-HIV drugs interrupt. It's "a natural preventative to HIV," says Sodroski.

Nearly a dozen other labs have hunted for this blocking agent, and some close competitors are swallowing hard as they're applauding. "I'm sick as a dog, because it's a beautiful piece of work," says Paul Bieniasz of the Aaron Diamond AIDS Research Center in New York City. "Whether it can be harnessed to combat HIV is uncertain at present, but even if it is just a novel basic research finding, it's a completely new system of antiviral cellular activity." Stephen Goff, whose lab at Columbia University reported the discovery of a rat cellular protein with antiviral activity (*Science*, 6 September 2002, p. 1703), says he's particularly excited by the Sodroski lab's finding. "It opens up all sorts of new things," says Goff, who wrote a *Nature* News and Views article that accompanies the report. "The evidence is strong that this is a major restriction gene."

Sodroski and co-workers uncovered the protective protein by putting a wide variety of monkey genes into clones of human cells that they knew could support HIV's growth. Two of the clones they engineered became resistant to HIV, and they had only one monkey gene in common: the one coding for TRIM5-α. To show that removing this block still could tip the scales in favor of the human virus, "Animal models are never perfect imitations of the real thing, but if we had an HIV-like virus that could infect macaques, it would allow us to explore whether his lab can engineer an HIV capable of bypassing the monkey TRIM5-α, which could provide an extremely valuable new animal model. Currently, the main monkey model used by AIDS researchers relies on infecting rhesus macaques with SIV, a simian cousin of HIV, or SHIV, a hybrid that Sodroski helped concoct that has HIV's shell and SIV's core. Most anti-HIV drugs have little activity against either SIV or SHIV, and AIDS vaccine developers also would welcome a test virus that more closely resembles the human version. Although researchers suspect that TRIM5-α is but one of several factors that stop HIV from replicating efficiently in monkeys, removing this block still could tip the scales in favor of the human virus. "Animal models are never perfect imitations of the real thing, but if we had an HIV-like virus that could infect macaques, it would allow us to test hypotheses with respect to pathogenesis and vaccine development that you can't do with other models," says Sodroski. "It's certainly a reasonable goal, and it's much more achievable now."

—*MARTIN ENSERINK*