New research could help improve HIV/AIDS therapies

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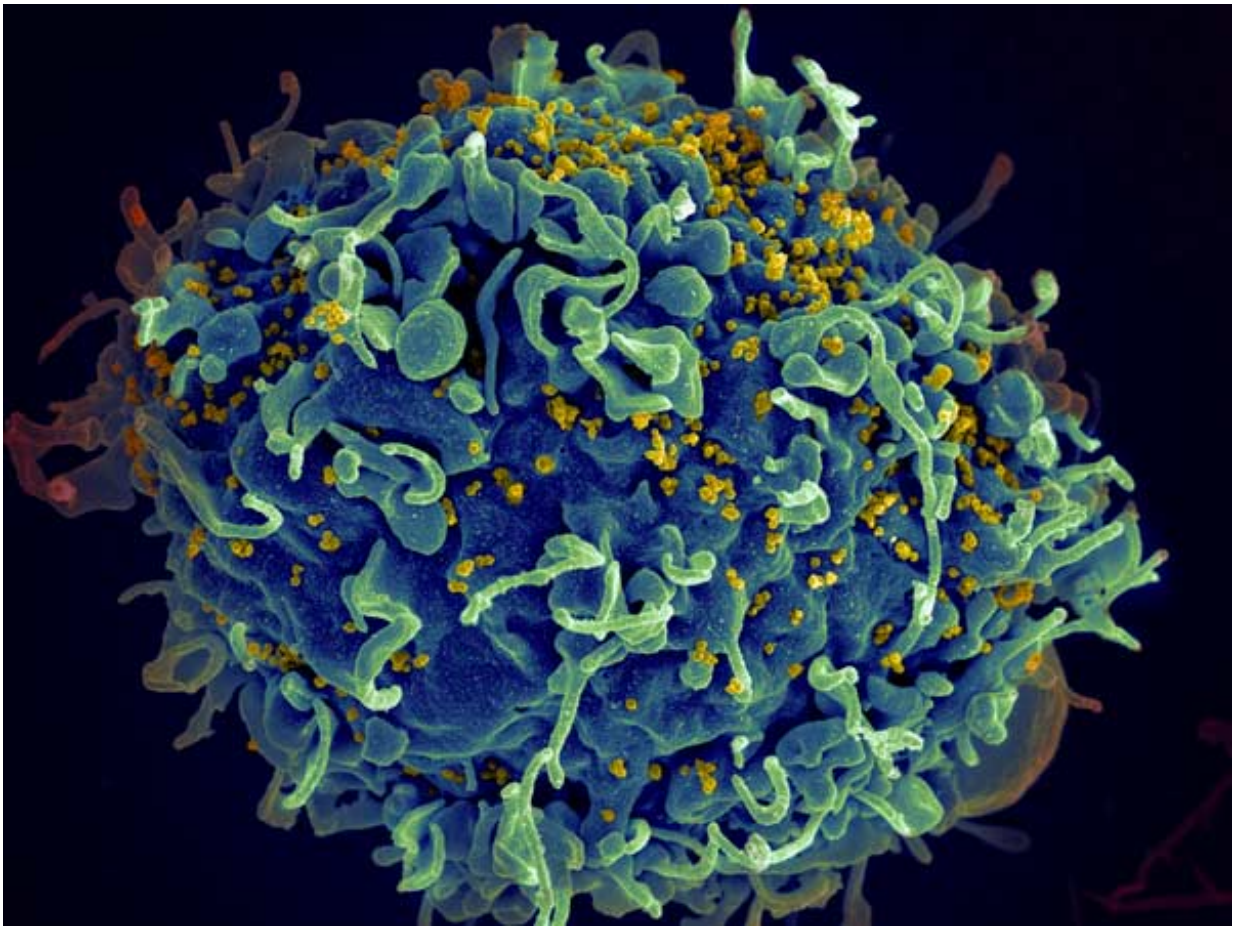

HIV (yellow) infecting a human immune cell. Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Hideki Aihara, Zhiqi Yin, and Ke Shi of the University of Minnesota, along with colleagues from Cornell University and St. Louis University have made a major stride in exploring new therapies to combat HIV/AIDS and retrovirus-based cancers. Reporting in the February 18 issue of the journal *Nature*, the researchers tell how an experimental procedure that involves beaming X-rays at immobilized molecules allowed them to discover how a cancer-causing retrovirus called RSV brings together many copies of a protein (known as integrase) to form tiny molecular claws that insert RSV genetic material into that of a host cell, conscripting it to make more retroviruses.

Because RSV is a close relative of the HIV-1 retrovirus, the work has potential application for improving HIV/AIDS therapies.

"It can certainly help with the development of anti-retrovirals to target the integrase functions," says Aihara, senior author on the paper and an associate professor in the University's Department of Biochemistry, Molecular Biology, and Biophysics. "Ultimately, we want to inhibit HIV integration, and for that purpose we need to know HIV intregrase's complex structure."

To conduct the study, researchers had to first figure out how to make a stable protein-DNA complex just the right size for analysis and immobilize it in crystalline form—a process that took several years. Next they bombarded it with X-rays and captured data on how the X-rays ping around as they travel through the crystal. Once the X-ray-scattering patterns were available, it took another three years of complex calculations using the Minnesota Supercomputing Institute's state-of-the-art computing capabilities to derive from them the precise position and configuration of the freeze-framed molecules. In the end, they came up with a big surprise: Whereas other viruses use a complex of four integrase molecules to guide the host and viral DNA into position and connect them, RSV uses eight.

"The structure looked very different from what we anticipated," Aihara says. "Initially it looked odd, but we started looking into details and it sort of all made sense."

Aihara now has his eye on doing the same things with HIV integrase, which is more difficult to work with than RSV integrase, but would yield results even more useful for designing anti-HIV therapies. "We would really like to see whether this unexpected assembly is also the case for HIV," he says. "We think it is, but we [need] evidence."

More information: Crystal structure of the Rous sarcoma virus intasome, DOI: 10.1038/nature16950

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