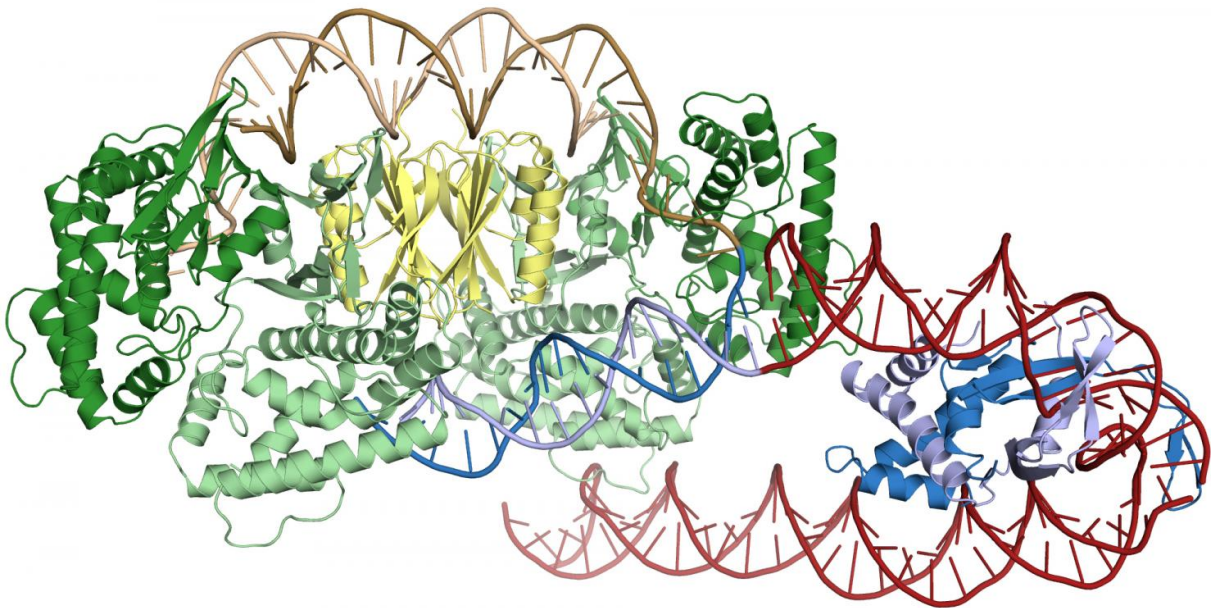


Researchers discover how CRISPR proteins find their target

July 20 2017



A protein called IHF (blue) creates a sharp turn in the DNA upstream of the CRISPR repeat, allowing Cas1-Cas2 (green and yellow) to recognize and bind the insertion site. Credit: Addison Wright, UC Berkeley

Researchers at the University of California, Berkeley, have discovered

how Cas1-Cas2, the proteins responsible for the ability of the CRISPR immune system in bacteria to adapt to new viral infections, identify the site in the genome where they insert viral DNA so they can recognize it later and mount an attack.

These proteins, which were recently used to encode a movie in the CRISPR regions of bacterial genomes, rely on the unique flexibility of the CRISPR DNA to recognize it as the site where viral DNA should be inserted, ensuring that "memories" of prior [viral infections](#) are properly stored.

The paper, which will be published online July 20 in *Science* by Jennifer Doudna and her research group, used electron microscopy and x-ray crystallography, performed at the Advanced Light Source at Lawrence Berkeley National Laboratory, the Stanford Linear Accelerator Center, and the HHMI electron microscope facility at UC Berkeley, to capture structures of Cas1-Cas2 in the act of inserting viral DNA into the CRISPR region.

The structures reveal that a third [protein](#), IHF, binds near the insertion site and bends the DNA into a U-shape, allowing Cas1-Cas2 to bind both parts of the DNA simultaneously. The lead authors, graduate student Addison Wright and postdoctoral fellow Jun-Jie Liu, along with co-authors Gavin Knott, Kevin Doxzen and Eva Nogales, discovered that the reaction requires that the target DNA bend and partly unwind, something that only occurs at the proper target.

CRISPR systems are a bacterial immune system that allows bacteria to adapt and defend against the viruses that infect them. CRISPR stands for clustered regularly interspaced short palindromic repeats and refers to the unique region of DNA where snippets of viral DNA are stored for future reference, allowing the cell to recognize any virus that tries to re-infect. The viral DNA alternates with the "short palindromic repeats",

which serve as the recognition signal to direct Cas1-Cas2 to add new viral sequences.

Specific recognition of these repeats by Cas1-Cas2 restricts integration of viral DNA to the CRISPR array, allowing it to be used for immunity and avoiding the potentially fatal effects of inserting viral DNA in the wrong place, Wright said.

While many DNA-binding proteins directly "read out" the nucleotides of their recognition sequence, Cas1-Cas2 recognize the CRISPR repeat through more indirect means: its shape and flexibility. In addition to coding for proteins, the nucleotide sequence of a stretch of DNA also determines the molecule's physical properties, with some sequences acting as flexible hinges and others forming rigid rods. The sequence of the CRISPR repeat allows it to bend and flex in just the right way to be bound by Cas1-Cas2, allowing the proteins to recognize their target by shape.

Research from George Church's lab at Harvard University showed that the information-storing capabilities of Cas1-Cas2 can be repurposed for recording frames of a movie rather than viral sequences and could possibly be used for recording other sorts of information as well.

The discovery of how Cas1-Cas2 recognize their target opens the door for modification of the proteins themselves. By tweaking the proteins, researchers might be able to redirect them to sequences other than the CRISPR repeat and expand their application into organisms without their own CRISPR locus.

More information: J.A. Doudna at Innovative Genomics Institute at University of California, Berkeley in Berkeley, CA et al., "Structures of the CRISPR genome integration complex," *Science* (2017).

[science.sciencemag.org/cgi/doi ... 1126/science.aao0679](https://science.sciencemag.org/cgi/doi/10.1126/science.aao0679)

Provided by University of California - Berkeley

Citation: Researchers discover how CRISPR proteins find their target (2017, July 20) retrieved 10 May 2024 from <https://phys.org/news/2017-07-crispr-proteins.html>

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