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CRISPR-Cas systems enable bacteria to acquire immunity against their viruses by capturing snippets of their DNA and using RNA-guided nucleases that cleave the viral DNA. Marraffini investigates the molecular mechanisms that make CRISPR immunity possible, and also explores genome editing and other potential applications for CRISPR-Cas systems.

In many bacteria and most archaea, CRISPRs—clustered, regularly interspaced, short palindromic repeats—constitutes that protects cells from phages and conjugative plan adaptive immune system that protects cells from phages and cojugative plasmids. Within CRISPR sites, the repeats are separated by short spacer sequences that match phage or plasmid genomes and specify the targets of interference.

Spacer sequences are transcribed into CRISPR RNAs (crRNAs)—small RNAs that, through base-pairing interactions with the target sequence, guide Cas nucleases to the invasive nucleic acid. Upon infection, CRISPR arrays can acquire new spacer units that match the sequence of the infecting phage or plasmid. In this way, CRISPR-Cas systems provide adaptive and inheritable immunity to the bacterial cell. The spacer content of CRISPR arrays reflects the many different invaders encountered by the host and can be expanded rapidly in response to new ones. Accordingly, CRISPR loci constitute a form of genetic memory that ensures the rejection of new, returning, and ever-present invading DNA molecules.

Marraffini uses *Staphylococcus epidermidis* and *Streptococcus pyogenes* as model systems for studying CRISPR immunity. The clinical isolate *S. epidermidis* RP62a harbors a CRISPR spacer that matches a sequence present in nearly all staphylococcal conjugative plasmids carrying antibiotic resistance genes and prevents their spread. Using this system, Marraffini revealed that the CRISPR-Cas machinery targets DNA, rather than RNA, directly. Work in the Marraffini lab also demonstrated that the *S. pyogenes* crRNA-guided Cas9 DNA nuclease constitute a formidable tool for genetic engineering.

His current research employs molecular genetic, biochemical, and structural approaches to analyze the genesis and function of CRISPR-Cas systems and discover novel immune systems of prokaryotes. Marraffini hopes to answer fundamental questions about how CRISPR-Cas systems destroy their targets, how the genetic memory is generated, how these systems interact with other bacterial defenses and ultimately understand how CRISPR-Cas immunity affects the evolution of bacteria and archaea.

EDUCATION

Lic. in biotechnology, 1998
University of Rosario

Ph.D. in microbiology, 2007
University of Chicago

POSTDOC

Northwestern University, 2008–2010

POSITIONS

Assistant Professor, 2010–2016
Associate Professor, 2016–2018
Professor, 2018–
The Rockefeller University

Investigator, 2018–
Howard Hughes Medical Institute

AWARDS

RNA Society Award, 2010

Searle Scholar, 2011

Rita Allen Foundation Scholar, 2012

NIH Director's New Innovator Award, 2012

The Rockefeller University Distinguished Teaching Award, 2013

40 Under 40, *Cell*, 2014

Hans Sigrist Prize, 2015

Earl and Thressa Stadtman Scholar Award, 2016

Howard Hughes Medical Institute-Simons Faculty Scholar, 2016

Albany Medical Center Prize in Medicine and Biomedical Research, 2017

Gabrielle H. Reem and Herbert J. Kayden Early-Career Innovation Award, 2017

NIH Director's Pioneer Award, 2017

Max Planck-Humboldt Medal, 2020

Genetics Society of America Medal, 2024

Vilcek Prize in Biomedical Science, 2024

SELECTED PUBLICATIONS

Baca, C.F. et al. Cat1 forms filament networks to degrade NAD+ during the type III CRISPR Cas antiviral response. *Science* 388, eadv9045 (2025).

Hossain, A.A. et al. DNA glycosylases provide antiviral defence in prokaryotes. *Nature* 629, 410–416 (2024).

Aviram, N. et al. Cas10 relieves host growth arrest to facilitate spacer retention during type III-A CRISPR-Cas immunity. *Cell Host Microbe* 32, 2050–2062 (2024).

Maguin, P. et al. Cleavage of viral DNA by restriction endonucleases stimulates the type II CRISPR-Cas immune response. *Molecular Cell* 82, 907–919 (2022).

Mo, C.Y. et al. Type III-A CRISPR immunity promotes mutagenesis of staphylococci. *Nature* 592, 611–615 (2021).