Sean F. Brady, Ph.D.

EVNIN PROFESSOR, LABORATORY OF GENETICALLY ENCODED SMALL MOLECULES

Natural products, especially genetically encoded small molecules, have a wide range of functions in biology and have proved very useful in the development of therapeutic agents. Brady's research centers on the discovery and characterization of new, genetically encoded small molecules from microbial sources, with a special focus on those produced by uncultured soil bacteria, human commensal bacteria, and pathogenic bacteria.

One of the key revelations originating from large-scale sequencing of bacterial genomic DNA is that the approaches traditionally used for identifying new natural products only provide access to a small fraction of the biosynthetic gene clusters present in nature. These studies indicate that essentially all bacteria—from those with fully sequenced genomes to those that have not yet been cultured—are rich sources of unstudied natural products.

Using methods from molecular biology, organic chemistry, and microbiology, Brady is working to access the biosynthetic gene clusters responsible for these previously inaccessible natural products. The development of methods to do so should significantly increase the number and diversity of natural products available to test as probes of biological processes and therapeutic agents.

Brady's first research focus is the development of new strategies for studying genetically encoded small molecules produced by bacteria that have not been grown in the lab. Soil microbes that have not yet been cultured outnumber their cultured counterparts by at least two to three orders of magnitude, making uncultured bacteria one of the largest pools of genetic diversity that remain unexamined for potentially useful natural products. Brady has worked extensively on the development of genetic strategies to access the vast chemical and biosynthetic potential of uncultured bacteria. His approach—which involves extracting this previously inaccessible DNA directly from environmental samples and cloning it in easily cultured bacteria—has allowed for the construction of large libraries of environmental DNA, as well as the development of methods to screen these libraries. His work has shown that these libraries are a promising source of both new derivatives of pharmacologically important classes of natural products, as well as completely novel families of bioactive natural products.

Brady's group is now mapping the presence of promising microbial gene clusters found in soil samples collected around the world. These maps may help guide the discovery of natural products by directing investigators to certain regions and environments.

The second focus of the Brady lab pertains to the chemistry of human microbiome-associated and pathogenic bacteria. It could one day lead to a better understanding of how commensal bacteria interact with their human hosts, and potentially address the problem of drug-resistant pathogenic bacteria. Brady uses phenotypic screening and bioinformatics methods to examine the small molecules produced by commensal and pathogenic bacteria. By studying the complex collections of small molecules used by these bacteria, he hopes to gain new insight into how bacteria interact with the world around them, and draw from these insights to determine how to better control both commensal and pathogenic bacteria.

EDUCATION

B.A. in molecular biology, 1993
Pomona College

M.S. in organic chemistry, 1999
Ph.D. in organic chemistry, 2002
Cornell University

POSTDOC

Cornell University, 2002

POSITIONS

Fellow, 2002–2006
Harvard Medical School

Assistant Professor, 2006–2012
Associate Professor, 2012–2018
Professor, 2018–
The Rockefeller University

Early Career Scientist, 2009–2015
Howard Hughes Medical Institute

AWARDS

Sinsheimer Fund Scholar, 2007

Beckman Young Investigator, 2007

Irma T. Hirschl/Monique Weill-Caulier Trust Research Award, 2007

Searle Scholar, 2007

Kenneth Rainin Foundation Innovator Award, 2013

SELECTED PUBLICATIONS

Burian, J. et al. High-throughput retrieval of target sequences from complex clone libraries using CRISPR. *Nat. Biotechnol.* 41, 626–630 (2023).

Wang, Z. et al. Bioinformatic prospecting and synthesis of a bifunctional lipopeptide antibiotic that evades resistance. *Science* 376, 991–996 (2022).

Wang, Z. et al. A naturally inspired antibiotic to target multidrug-resistant pathogens. *Nature* 601, 606–611 (2022).

Li, L. et al. Identification of structurally diverse menaquinone-binding antibiotics with in vivo activity against multidrug-resistant pathogens. *Nat. Microbiol.* 7, 120–131 (2022).

Hover, B. et al. Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-positive pathogens. *Nat. Microbiol.* 3, 415–422 (2018).