Exploring siderophore scaffolds for antibacterial strategies

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Siderophores are Fe(III)-chelating secondary metabolites that bacteria deploy to acquire iron, an essential nutrient, from the vertebrate host. Our ongoing research interests include the design and evaluation of new antibacterial strategies that target the siderophores and siderophore transport machinery used by Gram-negative bacterial pathogens such as *Escherichia coli* and *Salmonella*.[1] These efforts focus on siderophore-antibiotic conjugates and siderophore-based immunization. Here, we present case studies that illustrate the design and evaluation of siderophore-antibiotic conjugates based on the catecholate siderophore enterobactin.[2,3] These conjugates harbor various antibacterial cargos including antibiotics with periplasmic or cytoplasmic targets. Our studies demonstrate conjugate transport by the enterobactin uptake machinery and the ability to target pathogenicity, provide insight into conjugate fate including the consequences of cellular processing, and illuminate antibacterial activity. These studies provide a guide for further investigations of targeting siderophores and siderophore uptake machinery in the design of non-traditional antibacterial agents.

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[3] W. Neumann, M. Sassone-Corsi, M. Raffatellu, E. M. Nolan *J. Am. Chem. Soc.* **2018**, *140*, 5193-5201.