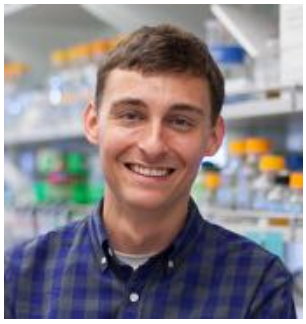
CHEMICAL ENGINEERING

DISTINGUISHED YOUNG SCHOLARS SERIES



CHRISTOPHER BAHL

Monday, July 10, 2017

Postdoctoral Fellow
University of Washington

De novo design of antivirulence therapeutics based on genetically encodable, hyperstable constrained peptides

ABSTRACT: Organisms from all domains of life produce ~20-50 residue disulfide-constrained peptides, with functions ranging from signaling to virulence and immunity. These peptides, which are stabilized in a functional conformation by disulfide bonds, possess many of the beneficial pharmacological properties of small molecule drugs (e .g . high stability, tissue penetrance), while retaining the high interaction specificity of larger biological drugs, such as antibodies. Thus, constrained peptides represent a largely untapped class of drug scaffolds, and they are genetically encodable. We have developed a generalized computational method for designing constrained peptides de novo , which provides access to much more molecular diversity than is currently available from naturalistic observation. We used the method to design constrained peptides spanning nine different structural topologies with sequences unrelated to known genes. The designed peptides contain up to three disulfide bonds, can be expressed and purified from bacteria, and exhibit high thermal and chemical stability. Experimentally determined X-ray and NMR models show that the design protocol has atomic-level accuracy. The new method enables design of peptides with structures custom-tailored to specific applications; current efforts to incorporate function are directed toward treating infectious disease by antagonizing the virulence-promoting mechanisms of pathogenic microorganisms. Our two primary targets are: the biofilm-regulating Lap system from Gram-negative bacteria, and super-antigenic enterotoxins secreted by Gram-positive bacteria. In each case, existing structural and mechanistic information is being leveraged in conjunction with computational peptide design to engineer site-specific protein-protein interactions with an intended therapeutic effect.

LECTURE 4:00 – 5:00 (PAA) A110
Happy Hour in Benson Hall Lobby Following

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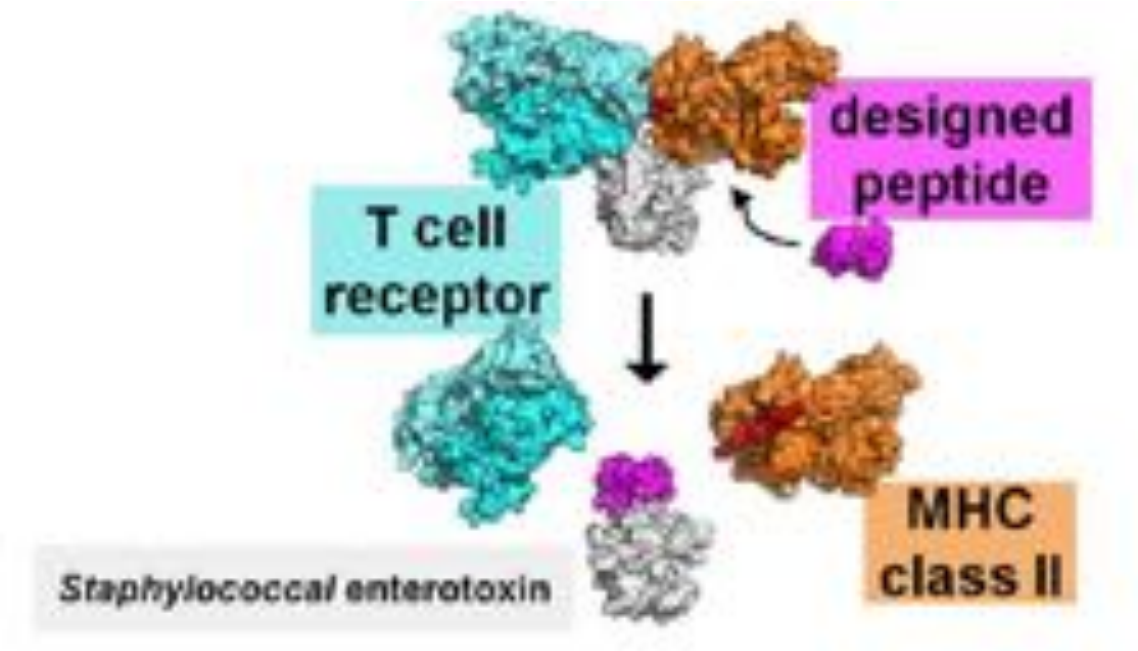

BIOGRAPHY: Dr. Christopher Bahl is a biochemist and protein engineer whose focus is understanding protein function-structure relationships. As a graduate student with Dean Madden at the Geisel School of Medicine, Chris studied a novel virulence factor from Gram-negative bacteria called Cif. He determined the structure of Cif, elucidating a heretofore unknown mechanism of bacterial pathogenesis, exploited this knowledge to reveal a family of virulence factors from related pathogens, and discovered and characterized a small-molecule inhibitor. In his current position as a postdoc with David Baker at the University of Washington, Chris developed and used computational methods to build genetically encodable, hyperstable, disulfide-rich peptides de novo, as well as expanded the laboratory toolkit necessary to produce these often-difficult proteins. Recently, Chris has been using these de novo peptides as scaffolds to engineer protein-based antagonists to bacterial virulence factors.