Advancing the Next Generation of Nucleic Acid Therapeutics

Prof. John C. Chaput

Department of Pharmaceutical Sciences,

University of California, Irvine

Abstract

Synthetic genetic polymers (XNAs) have the potential to transition nucleic acid molecules from laboratory tools to therapeutic agents, but additional progress is needed for such reagents to reach the clinic. In this talk, I will describe recent advances in the generation of XNA molecules that function with ligand binding and catalytic activity. The first half of the talk will focus on the evolution of a biologically stable artificial genetic system comprised of □-L-threofuranosyl nucleic acid (TNA) that facilitates the production of high quality protein capture reagents termed threomers. Threomers were discovered against two prototypical protein targets implicated in human diseases using uracil-modified nucleotides uniformly equipped with aromatic side chains commonly found in the paratope of antibody-antigen crystal structures. Kinetic measurements reveal that side chain modifications are critical for generating threomers with slow off-rate binding kinetics. The second portion of the talk will report on an XNA modified version of the classic DNAzyme 10-23, termed X10-23, that achieves multiple turnover activity under cellular conditions and resists nuclease digestion. The new reagent overcomes the problem of product inhibition that has limited previous 10-23 designs using molecular chemotypes that balance the dynamic properties of substrate binding with product release. In cultured mammalian cells, X10-23 facilitates persistent gene silencing by degrading endogenous mRNA transcripts with single-base discrimination. Together, these findings expand the chemical space of evolvable non-natural genetic systems to include functional groups that enhance protein target binding and RNA cleavage by mimicking the properties of protein-based antibodies and enzymes.

Biography

John Chaput is Professor of Pharmaceutical Sciences, Chemistry, and Molecular Biology and Biochemistry at the University of California, Irvine (UCI). He graduated in 1994 from Creighton University with a bachelor's degree in chemistry and earned his Ph.D. in 2000 from the University of California, Riverside. For his Ph.D. thesis, he studied the molecular recognition properties of unnatural nucleic acid polymers. Under the guidance of Chris Switzer, he designed, built, and characterized the first five-stranded DNA helix that self-assembles around a metal-nucleated iso-guanine motif. From 2000-2004, he was an HHMI Post-Doctoral Fellow in Prof. Jack Szostak's laboratory at Harvard Medical School. While at Harvard, he studied the de novo evolution of functional proteins by mRNA display and developed early methods for synthesizing artificial genetic polymers using commercial polymerases. In 2005, he began his independent academic career as an Assistant Professor of Chemistry and Biochemistry at Arizona State University (ASU). He was promoted to Associate Professor in 2011 and Full Professor in 2014. From 2005 to 2015, he was a core faculty member of the Biodesign Institute at ASU, and from 2011-2014 served as Deputy Director of the Center for Evolutionary Medicine and Informatics (CEMI). In 2015, he moved his laboratory to UCI, where he develops enzymes that can manipulate artificial genetic polymers (commonly referred to as XNAs) in a manner analogous to the enzymes provided by nature. The overarching goal of his research is to develop the next generation of diagnostic and therapeutic agents using XNAs that are biologically stable and responsive to Darwinian evolution. In 2018, he was elected a AAAS Fellow for distinguished contributions to the field of chemical biology, particularly for the development of engineered polymerases that enable the evolution of artificial genetic polymers.