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Engineering natural peptides for the discovery of novel anti-infectives

Interest in peptides has grown significantly in pharmaceutical research and development. Currently, more than 60 US FDA approved peptide-based drugs are on the market, and over 170 peptide therapeutics are undergoing clinical evaluation. The therapeutic potential of peptides is largely influenced by their physicochemical properties and proteolytic stability profiles. To enhance these profiles, various strategies have been developed, including chemical modifications such as macrocyclization, N-methylation, and substitution with N-substituted glycines (peptoids). These engineered peptides are capable of recognizing large surface areas on targets, including protein-protein interactions (PPIs) and phospholipid membranes, thus expanding their applicability within the “beyond rule of five” (bRo5) chemical space.

Overuse of conventional antibiotics and the slow pace of new antibiotic drug development contribute to antimicrobial resistance (AMR). Multidrug-resistant (MDR) infections pose a serious public health threat,

highlighting the urgent need for novel antibiotics. Antimicrobial peptides (AMPs) have emerged as a promising platform to fight against MDR bacteria ensuring broad-spectrum antimicrobial activity and relatively low resistance emergence, with over 27 AMPs in clinical development. However, most peptides are limited to local administration due to the intrinsic susceptibility against proteolysis. To address this, non-natural backbones have been designed to mimic AMP structures. With an engineered backbone based on oligo-N-substituted glycines, peptoids have been used to explore the potential utility as a novel anti-infective drug.

Date : 2024년 12월 5일 (목) 오후 5시

Venue : 과학관 B130호

Host : 연세대학교 화학과

