

THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

Bioprospecting And Application Of Prediction Algorithms For The Identification Of Novel Amphibian Antimicrobial And Antiviral Peptides

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Today's warfighter, whether they are deployed at home or abroad, faces an increased risk of exposure to bacterial and viral pathogens, including potential man-made biothreat agents. Moreover, these pathogens also pose a threat to the health and welfare of the civilian population. The rampant spread of antibacterial resistance poses a growing threat to the effectiveness of available antibiotics, which are fundamental to modern medical care, while the recent COVID-19 pandemic demonstrated the potential for new and emerging viruses to wreak havoc on global health and productivity. Existing drugs and therapeutic development strategies have proven insufficient against these challenges, resulting in the urgent need for new effective broad-spectrum antibiotics and antiviral therapeutics. Antimicrobial host defense peptides (AMPs) represent a rich resource that can be leveraged for the development of new broad-spectrum antimicrobial and antiviral therapeutics. AMPs are fundamental elements of innate immunity, with many peptides exhibiting broad spectrum activity, including both antibacterial and antiviral properties, and can employ multiple mechanisms of action. While thousands of AMPs have been identified, the diversity of peptides and species represented is limited. While frogs and toads have proven a rich source of diverse and broad-spectrum AMPs, contributing the majority of known vertebrate AMPs, very few salamander and caecilian peptides have been reported. Frog, salamander and caecilian evolution diverged over 250 million years ago. Recently, mucosal secretions from salamanders were found to exhibit potent antimicrobial properties. Thus, the dearth of known salamander and caecilian AMPs represents a significant gap in our understanding of AMP diversity, and hampers our ability to effectively leverage AMPs for the development of new antibacterial and antiviral therapeutics. We have developed a sample agnostic bioprospecting-based strategy to identify intact endogenous AMPs from biological samples using tandem mass spectrometry. We have employed our bioprospecting approach in the analysis of mucosal secretions from both salamanders and caecilian species, which has yielded hundreds of new peptide sequences. Peptide identification from these species, especially salamanders, is particularly challenging due to the evolutionary distances between species and the scarcity of applicable reported genomic and transcriptomic data from related species. As a result, we have taken a multilayered approach to analyzing the peptide sequences and identifying potential AMPs, which includes the use of web-based antimicrobial peptide prediction algorithms and our own antiviral prediction algorithm. Drawing from this pool of predicted antimicrobial and antiviral peptides, we selected peptides for further analysis and sequence verification. Through this effort, we have identified multiple novel antimicrobial and antiviral peptide candidates, for further evaluation and development.

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