COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Novel Immunopeptidomic/machine Learning Integrated Platform For Next Generation Chikungunya T Cell Priming Vaccine Development

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Background: Vaccine development for biothreat and biodefense pathogens faces significant challenges due to limited commercial interest. Traditional vaccines primarily focus on eliciting humoral antibody responses, which may not offer long-term or mutation-resistant protection. Targeting cellular immunity, particularly CD8+ T cell responses, could provide broad and durable immunological defenses. Emergex Vaccines is pioneering a novel approach, combining immunopeptidomics and machine-learning to identify naturally processed and presented, infectious pathogen-specific T cell epitopes, focusing on emerging viral threats including the alphavirus Chikungunya (CHIKV).
Purpose: Develop a potent CHIKV T cell priming (TcP) vaccine based on 1) the identification of virus-specific T cell epitopes, and 2) an optimized intradermal delivery system. Emergex has established a CHIKV peptide library and characterized peptide-candidates through bio-assays.
Objective: Using a proprietary immunopeptidomic approach, Emergex generated a CHIKV-specific library of peptide-candidates from virally infected cells across different infection time points. Combination of in silico MHC class-I peptide analysis with empirical tetramer binding experiments, the candidates have been screened and down-selected to proceed with efficacy and potency evaluation.
Rationale of the research: Emergex has extended this methodology to tackle various pathogens like flavivirus, influenza, betacoronaviruses, and intracellular bacterial infectious agents. The TcP vaccines are crafted to offer comprehensive immune defense at the cellular level, exhibiting inherent cross-protective capabilities, and enabling the utilization for both therapeutic intervention and preventive measures.
Methods: For this study, CHIKV (S27 central/east African genotype) was used to infect a human cell line model. MHC class I restricted viral peptides were identified from multiple time points post infection. Analysis was conducted using a high-resolution Orbitrap Eclipse Tribrid mass spectrometer in data-dependent analysis mode. MS/MS data was searched using multiple search algorithms against an in-house created virus and human database comprising of protein sequences. MS/MS derived viral peptides were characterized by a customized predicted algorithm, by in vitro binding assays, and through T cell functional cell-based efficacy assays.
Preliminary results/conclusions: The peptide library contains more than two hundred (8-15mers) CHIKV derived MHC class I peptides from early to late infection phases. A few hotspots (conservative structural and non-structural protein regions) have been mapped. Peptides have been identified to present across multiple infection timepoints, suggesting their potential use as vaccine candidates. Peptide-MHC binding scores have been validated in dual approaches: machine based deep-learning algorithm and binding assay. 11 peptides have been formulated and proved to encourage antigen-specific differentiation and CD8+ T cell response. Emergex's CHIKV T cell vaccine formulation will be finalized and further tested using in vitro animal models as well as toxicology studies.
Impact to the DTRA mission and warfighter: An Emergex fully synthetic T cell vaccine strategy offers a novel avenue for supporting the DTRA mission by explicitly targeting broadly protective T cell responses to infectious agents deemed as biothreats, while also potentially combating swiftly mutating or yet unidentified pathogens. This approach leverages the robust and enduring shield provided by T cell responses. By integrating immunopeptidomic and machine learning technologies, Emergex can pioneer sustainable and innovative medical countermeasures tailored to confront priority biothreats and biodefense agents.