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COMBINATION IMMUNOTHERAPY ENHANCED ANTI-TUMOR ACTIVITIES OF XBP1, CD138 AND CS1 ANTIGENS-SPECIFIC CD8+ CYTOTOXIC T LYMPHOCYTES AGAINST MULTIPLE MYELOMA AND SOLID TUMORS

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Background: A recently completed Phase I/2a trials using a HLA-A2 XBP1, CD138 and CS1 multipeptide vaccine in smoldering multiple myeloma (SMM) patients demonstrated induction of antigen-specific CD8+ memory CTL. The antigens-specific Th1 type responses were further enhanced in the patients in combination with lenalidomide, as evidenced by increased Tetramer+ CTL and functional immune responses. Beyond myeloma, the multipeptide vaccine is in clinical trial to treat the patients with triple negative breast cancer by overexpression of the antigens in various solid tumours.

Objective: To expand therapeutic opportunities beyond HLA-A2 specificity, we have identified novel immunogenic peptides to HLA-A24 molecule, which is the second most dominant MHC Class I molecule in North America and the most frequent MHC Class I molecule in Asia.

Findings: Individual HLA-A24 peptides, XBP1 $UN_{185-193}$ (I S P W I L A V L), XBP1 $SP_{223-231}$ (V Y P E G P S S L), $CD138_{265-273}$ (I F A V C L V G F) and $CS1_{240-248}$ (L F V L G L F L W), induced the antigens-specific CTL with anti-tumour immune responses against both MM and solid tumours in an HLA-A24 restricted manner. CTL phenotypic characterization revealed the upregulation of immune costimulatory (OX40, GITR) and checkpoint antigens (PD1, CTLA, LAG3, TIM3). Peptide-specific CTL treated with clinical grade anti-OX40 or anti-PD1 displayed enhanced cytotoxicity and Th1 cytokines production to tumour cells. Furthermore, the central memory ($CD45RO^+CCR7^+$) CTL subset demonstrated enhanced functional activities to the respective tumour cells, with the highest increases induced by the OX40 stimulation or PD1 inhibition.

Significance: These results highlight the potential therapeutic application of a cocktail of HLA-A24 XBP1/CD138/CS1 peptides to evoke the antigens-specific CTL with a broad spectrum of responses against tumor and provide the framework for a combination immunotherapy with multipeptide vaccination and immune agonist or checkpoint inhibitor to inhibit immune suppression and enhance tumor-specific memory CTL activities in cancer patients.

Biography

Jooeun Bae has completed her PhD from Virginia Polytechnic Institute and State University and Postdoctoral studies from Harvard Medical School (Boston, MA) and Rush University Medical Center (Chicago, IL). She worked as an Assistant Professor at Rush University Medical Center, Senior Research Scientist at Cell Genesys Inc. (San Francisco, CA) and currently working as an Instructor at Dana-Farber Cancer Institute, Harvard Medical School. Her expertise has been Cancer Immunology and Immunotherapy, focused on discovery and development of cancer vaccine, which are currently in multiple clinical trials. She has published more than 22 papers in reputed journals and has been serving as an Editorial Board Member of repute.

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