THE ANTI-TUMOR ACTIVITY OF HSP-90 THERAPEUTIC CANCER VACCINE (AST-021P) COMBINE WITH TLR2/3 AGONIST IN A MMTV-NEU TRANSGENIC MODEL

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Background AST-021p, which is derived from HLA class II binding epitopes of human HSP90 protein, is an investigational therapeutic cancer vaccine for the malignant neoplasms. AST-021p is designed to demonstrate the immunologic efficacy by activating antigen-specific CD4+ Th1 cell in humans. Due to their ability to link the innate with the adaptive immune response, Toll-like receptor (TLR) agonists are highly promising as adjuvants in vaccines against life-threatening and complex diseases such as cancer, AIDS and malaria. In this study, AST-021p was investigated to evaluate the immunogenicity and tumor growth inhibitory effect under the condition of combining with various immune adjuvants derived from TLR agonists, using in-vivo model.

Methods Three different agonists of TLR (TLR-4, TLR-2/3, TLR-7/8) were assigned to investigate the immunogenicity in each group (4 FVB mice/group, total 4 groups). AST-021p was intradermally injected 3 times with different TLR-agonists and the immunogenicity was assessed from mouse splenocyte by HSP90-specific IFN- γ ELISpot method. We also examined the efficacy of AST-021p and selected TLR-agonist in MMTVneu Tg mice (4 mice/group, conducted twice and A total 8 mice was assigned to each group). The combination of AST-021p and TLR-2/3 agonist (AST-021p plus TLR-2/3 agonist) was injected 3 times every 10 days to mice followed by inoculated mouse mammary cancer cell line. The tumor volume change and immunogenicity were evaluated.

Results The most effective TLR-agonist as a potent immune adjuvant was a TLR-2/3 agonist (L-pampoTM, supplied by CHA Vaccine Institute). In MMTV-Neu transgenic mice, AST-021p (100 μ g) plus TLR-2/3 agonist significantly enhanced immunogenicity by increasing up to 130 ± 10 HSP-90 epitope specific T cells per 1×10^5 splenocytes ($P < 0.001$). AST-021p plus TLR-2/3 agonist also showed higher tumor growth inhibitory effect (170 ± 108 mm³) on post-implantation 35th day by suppressing mouse mammary cancer cell line (5×10^5)-derived tumor growth, compared with a TLR-2/3 agonist alone (1031 ± 450 mm³).

Conclusions Combination regimen of AST-021p and TLR-2/3 agonist (as immune adjuvant) demonstrated significant immunogenicity and tumor prevention effect in in-vivo study. These data supported the clinical study of AST-021p combined with TLR-2/3 agonist as active immune adjuvant in certain tumor types, and phase 1/2 clinical program would be expected to be initiated.

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Trial Registration Not applicable

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Ethics Approval All experimental procedures involving mice were performed with the guidance protocols approved by the Institutional Animal Care and Use Committee of Korea University (IACUC, Approval number: KOREA-2019-129)

Consent It is not an abstract containing sensitive or identifiable information.

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