CCL21 And Checkpoint Inhibitors For The Treatment Of Cancer

Tech ID: 29788 / UC Case 2018-912-0

SUMMARY
Researchers at the UCLA David Geffen School of Medicine have demonstrated a combination therapy of intratumoral administration of CCL21-gene modified human monocyte-derived dendritic cells and intravenous administration of anti-PD-1 inhibitor enhances tumor CD8+ T cell infiltration and reduces tumor growth.

BACKGROUND
Checkpoint antibody inhibitors, such as anti-programmed death-1 receptor/programmed death-ligand 1 (anti-PD-1/PD-L1) elicit promising antitumor responses in the treatment of a broad spectrum of cancers, through modulation of immune cell-tumor cell interaction. However, the majority of the patients exhibit poor clinical responses to PD-1/PD-L1 inhibitor treatment due to primary, adaptive, or acquired resistance to the treatment. Thus, an effective cancer immunotherapy requires methods to restore deficits in tumor antigen presentation and functional antitumor effector activities.

CCL21 is a secondary lymphoid chemokine that, upon binding to the CCR7 gene receptor, functions as a chemo-attractant for mature dendritic, naïve, and memory T cells, enhancing cell-mediated immunity against tumor cells. Intratumoral administration of CCL21 gene-modified dendritic cells (AdCCL21-DC) leads to increases of CD4+, CD8+, and CD11c+DEC205+ DCs infiltration of the tumor, decrease of immune-suppressive molecules in the tumor microenvironment, as well as reduction of tumor burden in murine lung cancer model. More importantly, intratumoral administration of AdCCL21-DC also enhances CD8+ T cell infiltration and increased tumor PD-L1 expression in advanced non-small cell lung cancer (NSCLC) patients.

INNOVATION
Researchers at UCLA have shown that advanced NSCLC patients with baseline PD-L1 expression benefit the most from anti-PD-1 treatment, suggesting responses to PD-1/PD-L1 blockade are more likely in the setting of tumor PD-L1 expression and a pre-existing T lymphocyte infiltration of the tumor. Indeed, these researchers have shown that AdCCL21-DC and anti-PD-1 combination therapy outperforms both mono-therapies in syngeneic murine lung cancer models. Specifically, the combination therapy significantly enhances the cytolytic activity of tumor-infiltrating lymphocytes (TILs) against tumor, accompanied by significant reduction in tumor volume and tumor growth.

APPLICATIONS
Immunotherapy for NSCLC, melanoma and other types of solid tumors.

ADVANTAGES

- Improve clinical response to anti-PD-1/PD-L1 therapy
- Boosts local and systemic immune responses
- Reduce tumor burden and tumor growth

STATE OF DEVELOPMENT
Completed pre-clinical studies in murine lung cancer models and phase I trials. The combination trial with anti-PD1 is starting now.

PATENT STATUS

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<tr>
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<td>China</td>
<td>Published Application</td>
<td>2019/217898</td>
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Additional Patent Pending

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ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

• Combination Immunotherapy