If a gene is required for tumor cell proliferation, knocking down the gene by siRNA should decrease cell survival and proliferation. We looked at both viability and apoptosis by caspase 3/7 activation after siRNA knockdown. We selected those antigens for which: [(mean of viability in NSCLC cell line) / (mean of viability in the normal lung cell line)] < 0.75 with a p-value of 0.1. We identified 14 candidates that are overexpressed in lung cancer and necessary for tumor cell survival. We have prioritized those proteins that have been previously described to play a role in lung cancer invasion, proliferation, metastasis, or survival. We selected 5 candidates to move forward: FKBP3, PARP1, RAN, S100A6, and SART3. An effective anticancer immune response needs to elicit a strong inflammatory Th1 response and avoid a Th2 response that promotes tumor tolerance. We used web-based modeling to predict epitopes that preferentially elicit a Th1 response, and assessed the presence of Th1 and Th2 responses via IFN-g (Th1) and IL10 (Th2). Six to seven epitopes (15-20 mer peptides) per antigen were evaluated by IFN-g and IL10 ELISPOT. Th1 epitopes identified in NSCLC antigens are the base for a preventive vaccine for NSCLC. The efficacy of the multiantigen Th1 vaccine to prevent lung cancer is currently under evaluation in the NTCI-induced lung cancer mouse model.

A35
Dendritic Cell in Situ Vaccination Potentiates Anti-PD-1 Efficacy and Induces Immunoediting in a Murine Model of NSCLC

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Studies reveal that responses to checkpoint blockade in non-small cell lung cancer (NSCLC) are associated with high tumor mutational burden (TMB), preexisting CD8+ T-cell infiltration, and high baseline PD-L1 expression within the tumor microenvironment (TME). In contrast, co-occurring KRAS/LKB1 mutation is associated with primary resistance to PD-1 blockade and decreased overall survival. In preclinical studies as well as a phase I clinical trial, we have discovered that intratumoral (IT) vaccination with gene-modified dendritic cells expressing CCL21 (CCL21-DC) promotes tumor effector T-lymphocyte infiltration, PD-L1 upregulation, and systemic tumor-specific immune responses. We hypothesized that in situ vaccination with CCL21-DC could restore tumor antigen presentation and promote T-cell priming and activation, thereby sensitizing nonresponsive NSCLC tumors to checkpoint blockade. Although genetically engineered murine models (GEMMs) of NSCLC bear driver mutations of the disease, recent studies reveal that these GEMMs possess low mutational burden. We established novel GEMMs of NSCLC [KrasG12D (K), KrasG12D/P53+/− (KP), KrasG12D/P53+/−/Lkb1+/− (KPL)] bearing common driver mutations and varying mutational loads by in vitro exposure of tumor cell lines to the carcinogen N-methyl-N-nitrosourea (MNU). Our preclinical KPL model with high TMB recapitulates the immunologic phenotype of human disease, and contains a predominance of myeloid-derived suppressor cells (MDSC), low tumor-infiltrating lymphocytes (TILs), and low PD-L1 expression within the TME. As anticipated, the KPL tumors are resistant to anti-PD-1 therapy, even with increased mutational load. We evaluated IT CCL21-DC combined with anti-PD-1 therapy in immunocompetent mice bearing KPL tumors with high TMB, and observed that IT CCL21-DC vaccination induces infiltration of autologous T lymphocytes and conventional type 1 DCs (cDC1s) into the TME and sensitizes the tumors to anti-PD-1 therapy. Combination therapy also reprogrammed the myeloid compartment, resulting in a significant reduction of MDSCs and a concurrent increase in CD11b+Ly6G+Ly6C+ monocyte/myeloid population. Whole-exome sequencing (WES) of tumors revealed immune-editing and selective depletion of tumor subclones post IT CCL21-DC and anti-PD1 combination therapy. Future studies will evaluate the evolution of the T-cell receptor (TCR) repertoire in response to the combination treatment and define functional responses to neoepitopes. These studies will enhance our understanding of the molecular mechanisms of tumor vaccination and facilitate the development of rational combination strategies.

A36
Patient-Specific Humanized PDX Model for Overcoming Tumor Resistance to Immune Checkpoint Inhibitors in NSCLC Patients

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Background: Lung cancer is the most common cause of cancer-related mortality worldwide. Over the past few years, immune checkpoint inhibitors (ICI) have been shown to provide unprecedented clinical success in non-small cell lung cancer (NSCLC). However, ICI have some drawbacks, including initial and acquired resistance, which was observed after a complete response during and after previous ICI treatment. This relapse phenomenon was suggested to be associated with the state of the immune system and the tumor-immune response microenvironment interaction. The critical observation of cancer resistance or progression under ICI treatment suggests that a better and deeper understanding of the dynamic responses between the antitumor immune system and the tumor interaction, as it accrues in the patient setting, is therefore of utmost importance. Methods: Using a patient-specific humanized patient-derived xenograft (PDX) (huMicX) model, we will study the coevolution between tumor and the immune system with and without ICI intervention. Comprehensive OMICS analysis on the proteomic, transcriptomic, and genomic levels will be performed on samples collected from human patients and the huMicX model. Results: Sample biobank of whole blood and tumor tissues, and consensus protocols for peripheral HSC CD34+ isolation, are being established from NSCLC patients. Tumor tissue samples have been used to generate a PDX in mice model. Data from PDX models have demonstrated the feasibility of testing the activity of autologous transplanted lymphocytes against the patient’s tumor in vivo with a clinical benefit in the same patient overcoming ICI resistance. Conclusion: The huMicX model is designed to provide vital knowledge of the patient-specific tumor and immune system microenvironment, and the dynamic assessment of the mechanisms of ICI tumor resistance. This preclinical model is expected to present both treatment intervention and prognostic or predictable biomarkers, which will be exploited subsequently in actual clinical settings.

A37
N-803 Plus Nivolumab for Advanced or Metastatic Non-Small Cell Lung Cancer: Update on Phase II Experience of Combination PD1 Blockade with an IL-15 Superagonist

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Immunotherapy has radically altered the treatment landscape of non-small cell lung cancer (NSCLC), yet the majority of patients treated with