Inhaled Lipid Reducing Agents to Restore Anti Tumor Immunity and Enhance Immunotherapy in Aged Lung Cancer Patients

Mechanistically-defined, localized, and repurposed immuno metabolic precision therapy that overcomes age related resistance to immune checkpoint and targeted therapies in non small cell lung cancer (NSCLC).

Technology

NYU innovators developed a therapeutic strategy to use inhaled lipid-reducing agents to restore anti-tumor immunity and enhance immunotherapy in aged lung cancer. They uncovered an aging associated lipid cascade that creates an immunosuppressive tumor microenvironment in the lung. Using naturally aged (~20-month-old) and airway epithelial cell (AEC)-specific senescence mouse models, organoid co-cultures, single-cell RNA-seq, spatial lipidomics, and adoptive transfer experiments, the innovators showed that senescent AECs upregulate lipid biosynthesis and cause arachidonic acid (AA) pathway activation in neighboring alveolar macrophages (AMs), thereby suppressing response to PD-1 blockade and KRAS(G12C) inhibition and promoting lung tumor growth. Upon genetic and pharmacological disruption of this AEC-lipid-AM axis, the innovators found diminished AA metabolites, rebalanced immune cell composition, enhanced tumor cell apoptosis, and improved PD-1 blockade and KRAS(G12C) inhibitor efficacy in aged mice. As an in vivo proof-of-concept study, the innovators demonstrated that inhaling the FDA-approved lipid-reducing agent simvastatin selectively reduces immunosuppressive myeloid populations in the lungs of aged mice.

Background

Non-small cell lung cancer (NSCLC) predominantly affects older adults. Age is associated with impaired adaptive immunity, chronic low grade inflammation, and inferior response to immune checkpoint inhibitors. Despite the clinical success of PD 1/PD L1 inhibitors and KRAS(G12C) targeted therapies, only a subset of patients enjoys durable benefit. Elderly patients often exhibit lower response rates and shorter survival. Clinical correlative data from NYU Langone Health show that NSCLC patients ≥75 years have inferior pembrolizumab outcomes. There is a need for a therapeutic strategy that improves therapeutic outcomes for older NSCLC patients.

Development Stage

The innovators have conducted in vivo mechanistic and proof-of-concept studies. They have planned in vivo therapeutic experiments to evaluate the therapeutic synergy between inhaled lipid reducers and immune checkpoint inhibitors in aged lung cancer models, as well as clinical data analyses to validate the working model.

Applications

Technology ID

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Category

Life Sciences/Biochemicals & Small Molecules

Life Sciences/Therapeutics/Oncology

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- **Therapeutic:** Lipid-reducing agents administered alone or in combination with immune checkpoint blockade and targeted therapies, especially in elderly NSCLC patients with mutated KRAS.
- **Diagnostic:** AA metabolites and other species in the AEC-lipid-AM axis could serve as biomarkers of aging-associated immunosuppression in the lung and predict response to immune checkpoint blockade and targeted therapies.

Advantages

- **Overcomes resistance to existing therapies:** Enhance efficacy and durability of PD 1/PD L1 inhibitors and KRAS(G12C) inhibitors in elderly NSCLC patients by reducing immuno-suppression.
- **Mechanistically-defined:** Directly targets an aging-associated immunosuppressive lipid cascade discovered and tested by the NYU innovators.
- **Precision medicine:** Personalized therapy based on NSCLC patient KRAS status, age, and immuno-metabolic biomarkers.
- **Easy, localized delivery:** Simvastatin can be inhaled, concentrating activity in the lung, minimizing toxicity relative to systemic regimens.
- **Repurposing of clinically familiar drugs:** Simvastatin is FDA-approved, potentially accelerating translation and lowering development risk.

Intellectual Property

NYU has filed a pending provisional patent application covering the pharmaceutical composition and method of combining lipid-reducing agents and immunotherapy agents to treat pulmonary disease.