Anti-LYPD3 CAR T-cell therapy for the treatment of squamous cell carcinoma

**Unmet Need**

Chimeric Antigen Receptor (CAR) T-cell therapy, a form of immunotherapy, has proven highly effective against blood cancers such as leukemias and lymphomas. This therapy uses T-cells that are genetically engineering *ex vivo* to activate the immune system, clear tumor cells, and improve patient outcomes. These engineered T-cells express a receptor to selectively recognize tumor surface antigens on one end and initiate a signaling cascade via an intracellular domain on the other end. However, the efficacy of CAR T-cell therapy against solid tumors remains limited. Solid organ tumors modify their surrounding environment to inactivate T cells. Further, the CAR-T cell therapy must target a protein specific to the tumor to prevent off target killing. Yet, 93% of new cancer cases in the US are solid organ tumors. One such example is squamous cell carcinoma which includes multiple tumor subtypes including in the head and neck, lung, esophagus, bladder, cervix, and skin. Squamous cell carcinoma is the second most common type of skin cancer in the US with more than 1 million cases diagnosed per year and current treatments primarily rely on performing micrographic surgery. There is a need for CAR T-cell therapies that can effectively target squamous cell carcinoma and thus, provide an immunotherapy alternative to surgery.

**Technology**

Duke inventors have developed a novel CAR T-cell therapy expressing a receptor for the Ly6/PLAUR domain-containing protein 3 (LYPD3). This is intended to be an immunotherapy treatment for patients with squamous cell carcinoma. Specifically, the inventors have identified LYPD3, a surface protein potentially
implicated in cell-matrix interactions and tumor progression, as preferentially overexpressed at the invasive front of various squamous cell carcinoma subtypes. As such, targeting LYPD3 could lead to tumor suppression with limited toxicity against non-tumor cells. This has been demonstrated through in vivo studies in mice with lung squamous cell carcinoma where this LYPD3 CAR T-cell therapy resulted in a substantial increase in tumor killing efficiency and a greater than 2-fold reduction in tumor size. Toxicity studies in mice further verified treatment tolerance in mice without loss in body weight.

**Other Applications**

The technology could also be adapted to target other cancers characterized by overexpression of the LYPD3 protein. Additionally, the technology could be combined with other immunotherapies or treatments for enhanced efficacy.

**Advantages**

- Effective immunotherapy alternative to surgery in patients with squamous cell carcinoma.
- Versatile treatment that can target multiple different subtypes of squamous cell carcinoma with the same therapy.
- Well-tolerated treatment in mouse models without severe side effects or weight loss.