

## MASTER'S THESIS

# Investigating Combined Gamma-delta T Cells and Immune Checkpoint Therapy Against Mesothelioma Via Pyroptosis in Vivo

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## ABSTRACT

Mesothelioma, a life-threatening cancer affecting the mesothelial lining of the pleura, peritoneum, and pericardium, poses significant treatment challenges. Primarily caused by asbestos exposure, this malignancy arises from the transformation of normal mesothelium cells into tumor cells. Unfortunately, available treatment options for patients are limited in extending their lifespan. However, there is hope in overcoming the tumor microenvironment's immunosuppressive effects induced by PD-1/PD-L1 through the use of gamma delta ( $\gamma\delta$ ) T cells. Specifically, a subset of  $\gamma\delta$  T cells known as V $\delta$ 2 T cells has demonstrated effectiveness against various cancers by infiltrating tumor masses. Thus, our hypothesis is that V $\delta$ 2 T cells can effectively kill mesothelioma.

In this study, we discovered that V $\delta$ 2 T cells possess the ability to kill mesothelioma cells, and their cytotoxicity can be further enhanced by using an anti-PD-1 antibody. To evaluate the therapeutic potential, we established mesothelioma xenograft mouse models by intrapleural injection into the pleural cavity. Through in vivo imaging, we detected luciferase activity in the tumor as early as 2 days post-tumor injection. At the experimental endpoint, tumors were observed in the mesothelium, pleural, and pericardial linings within the pleural cavity. Notably, adoptive transfer of V $\delta$ 2 T cells resulted in a 30-40% inhibition of mesothelioma development compared to the control group. Importantly, V $\delta$ 2 T cells successfully infiltrated into the tumor, with a higher propensity for areas containing BTN2A1<sup>+</sup> cells. Intriguingly, we detected cleaved gasdermin D in these cells, indicating the occurrence of pyroptosis. Live cell imaging revealed membrane blebbing, while increased levels of cleaved caspase 3 and gasdermin E were detected through Western blot analysis.

Therefore, this study provides compelling evidence that the combination of V $\delta$ 2 T cells and anti-PD-1 antibody can induce pyroptotic cell death in mesothelioma, offering a promising avenue for immunotherapy.