Tumor draining lymph nodes (TDLN) are the first site of metastasis in most types of cancer. The extent of metastasis in the lymph nodes is often used in staging cancer progression. We previously showed that nano scale TRAIL liposomes conjugated to human natural killer cells enhance their endogenous therapeutic potential in killing cancer cells cultured in engineered lymph node microenvironments. In this work, it is shown that liposomes decorated with apoptosis-inducing ligand TRAIL and an antibody against a mouse natural killer cell marker are carried to the tumor draining inguinal lymph nodes and prevent the lymphatic spread of a subcutaneous tumor in mice. It is shown that targeting natural killer cells with TRAIL liposomes enhances their retention time within the tumor draining lymph nodes to induce apoptosis in cancer cells. It is concluded that this approach can be used to kill cancer cells within the tumor draining lymph nodes to prevent the lymphatic spread of cancer.

**Clinical Significance of tumor cells in the lymph nodes**
- Several patients are diagnosed with cancer cells in the lymph nodes.
- Lymph nodes serve as bridgeheads for distant organ metastases.
- Metastasis in LN is often used in staging tumor progression.

**Study Design**
- Group 1: Buffer
- Group 2: Soluble TRAIL
- Group 3: TRAIL/IgG liposomes
- Group 4: Anti-NK1.1 liposomes
- Group 5: TRAIL/Anti-NK1.1 liposomes

**Results**
- TRAIL/Anti-NK1.1 liposomes can completely eliminate cancer cells in the TDLN.

**Conclusions**
- By targeting TRAIL liposomes to NK cells, their therapeutic potential is enhanced by presenting TRAIL in its natural form, bound to the surface of NK cells.
- TRAIL/Anti-NK1.1 liposomes can functionalize NK in mouse lymph nodes.
- Significant reduction in tumor burden was detected in mice.
- TRAIL liposomes conjugated to NK cells within the TDLN can prevent the metastasis of a subcutaneous primary tumor in mouse.