

Background

Tumor Suppressor Candidate 2 (TUSC2), located on chromosome 3p21.3, is frequently deleted in multiple human cancers, including non-small cell lung carcinoma (NSCLC), small cell lung carcinoma (SCLC), mesothelioma, breast cancer, and head-and-neck cancers. Loss of TUSC2 is associated with reduced survival and increased tumor aggressiveness. Although TUSC2 is known to suppress tumor cell proliferation and induce apoptosis, its regulatory role in the immune system—particularly in innate lymphoid populations—remains insufficiently defined. Building on our prior work identifying TUSC2 as a mitochondrial protein involved in calcium regulation and immune modulation, we hypothesized that TUSC2 exerts antitumor effects in part by enhancing NK cell cytotoxicity.

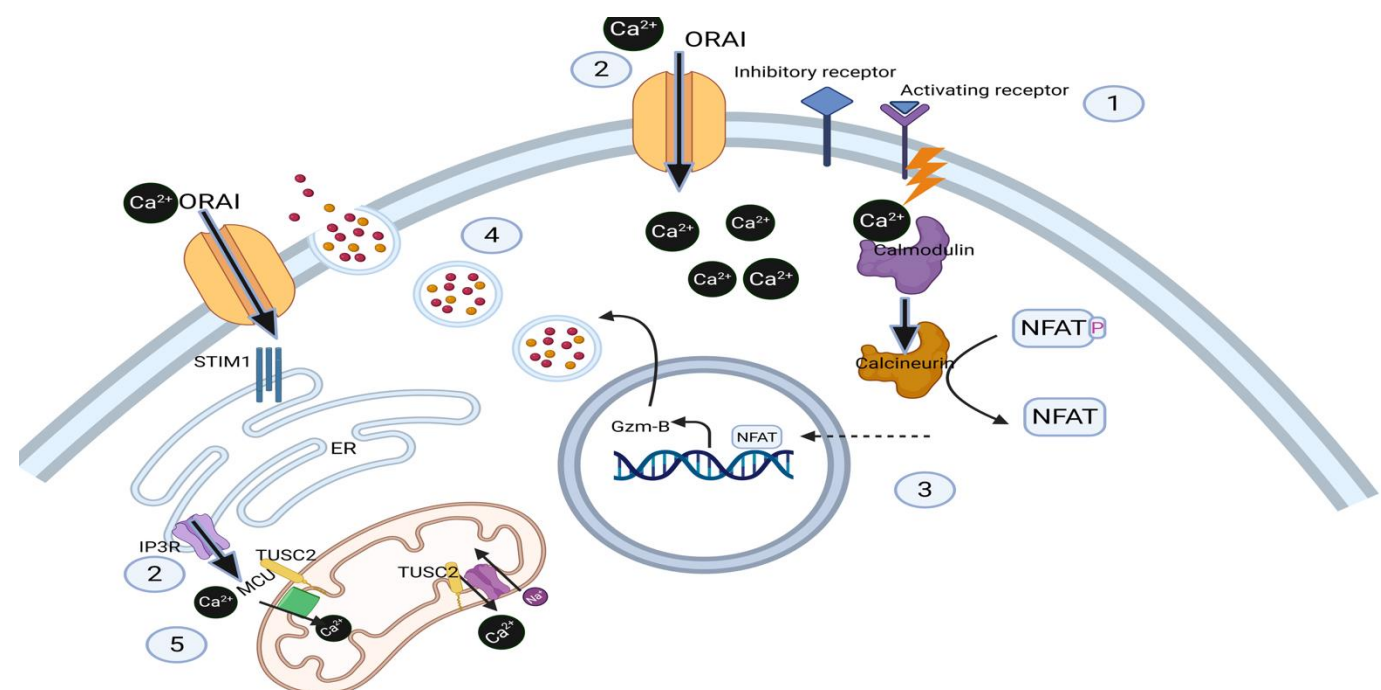


Figure 1: A schematic showing the importance of calcium in cytotoxic NK cell signaling

Aims

1. Explore the anti-tumor effect of TUSC2, leveraging the Tusc2 KO mouse model and TUSC2 expressing lipoparticles (Quar Oze)
2. Investigate the tumor microenvironment in mice that received TUSC2 supplementation versus the control group
3. Study cytotoxic immune cells, specifically NK cells, *in vitro* to identify the effect of Quar Oze on cytotoxic granules.

Research Design

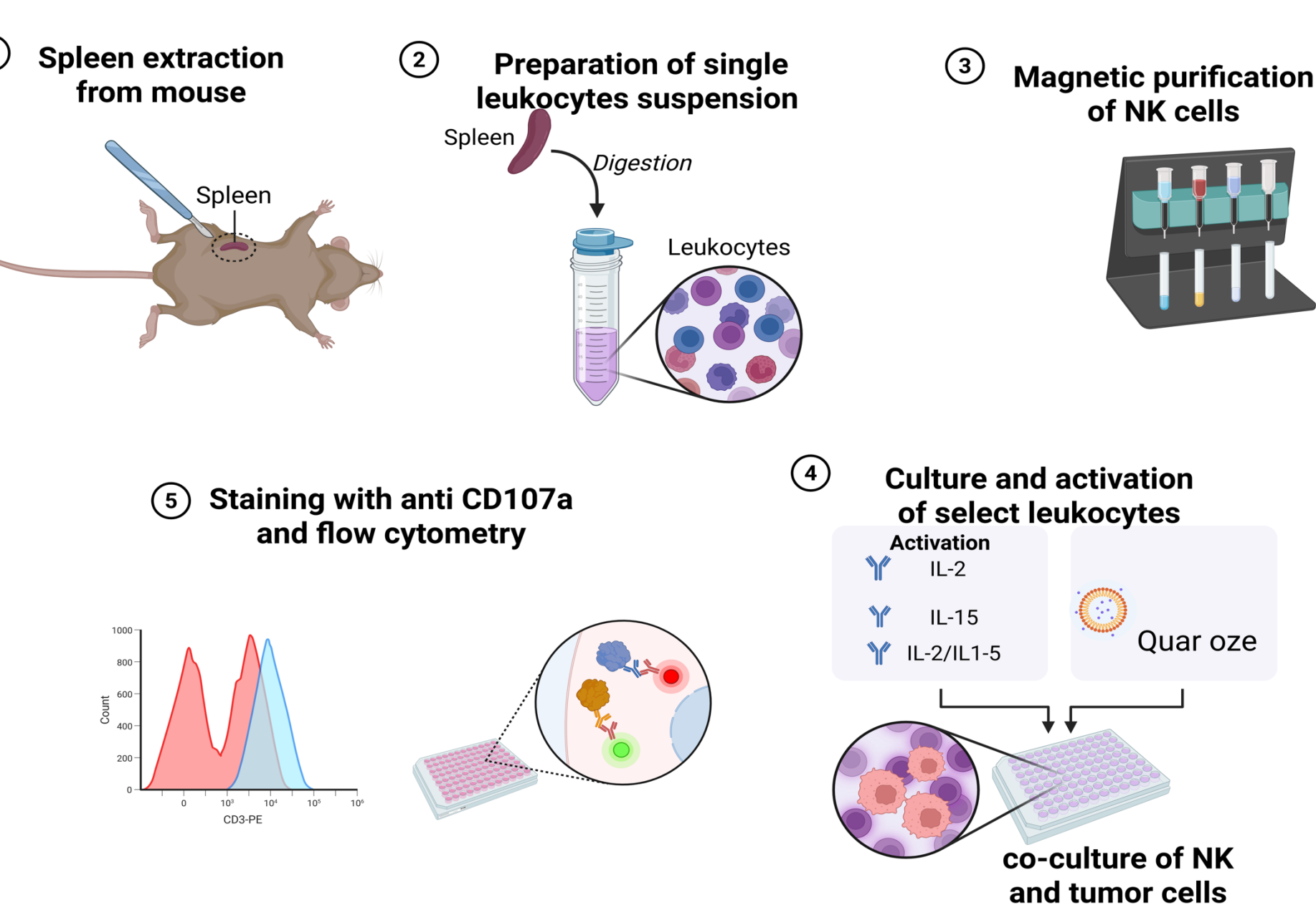
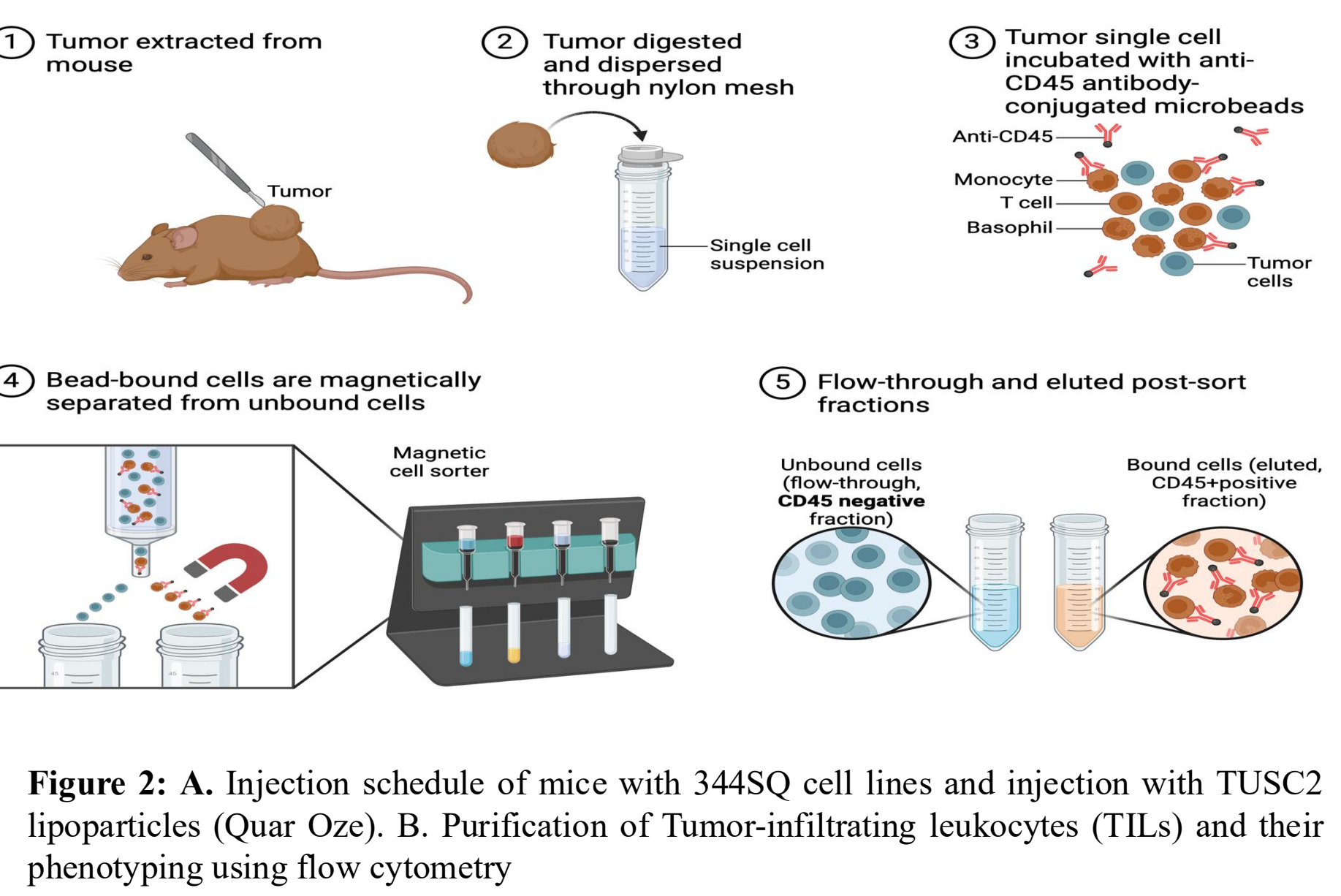
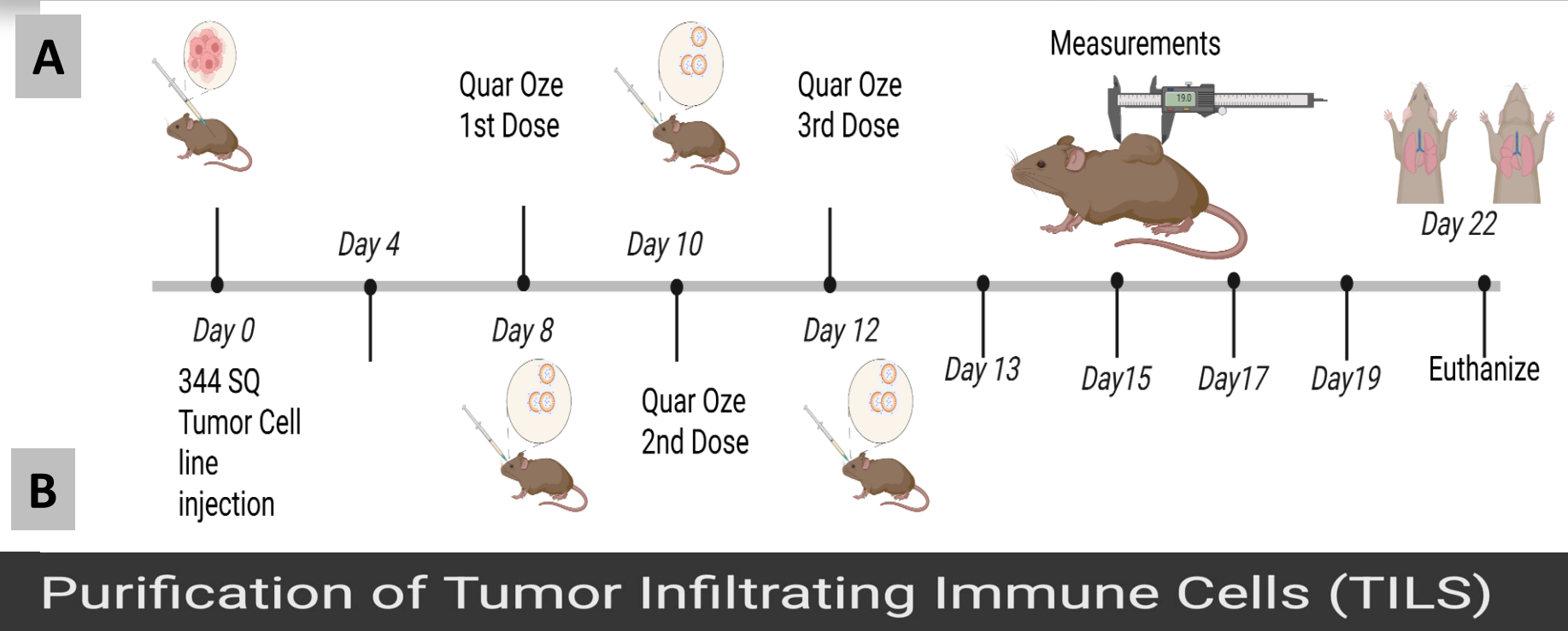


Figure 3: NK cell harvesting, purification and co-culture with 344SQ cell line

Results

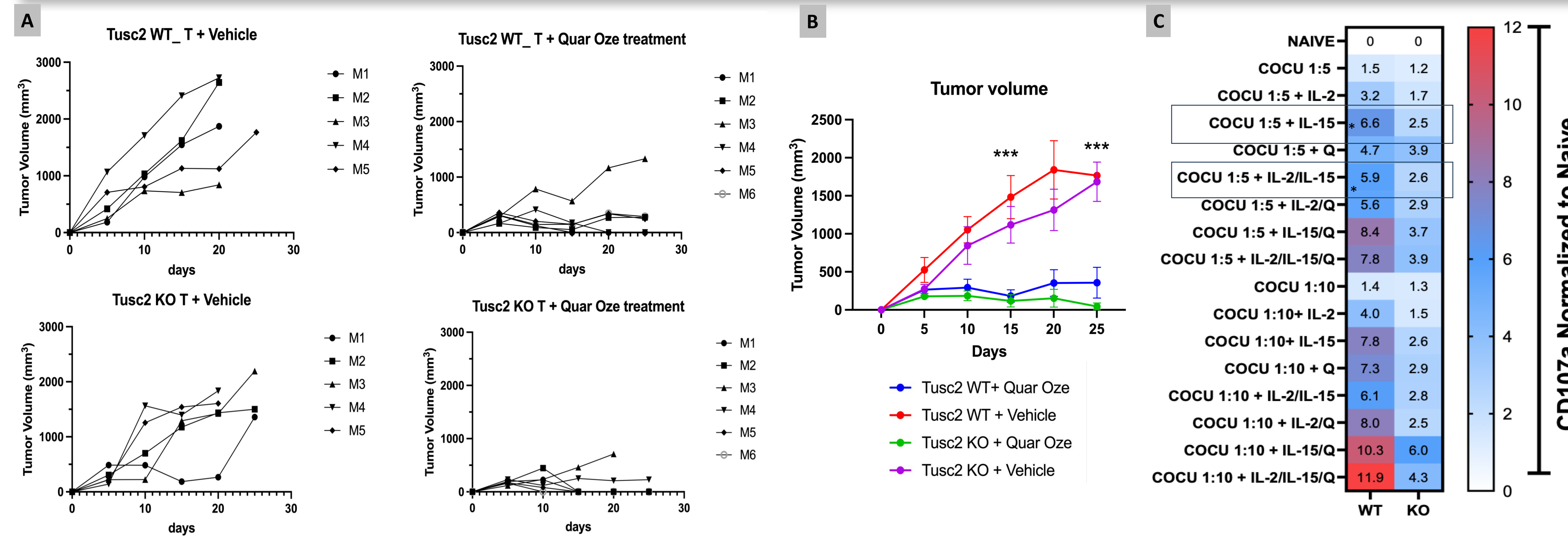


Figure 4: A. B. Treatment with TUSC2 lipoparticles (Quar Oze) significantly reduced tumor volume in both Tusc2 WT and KO mice. C. In vitro coculture of WT/ KO NK cell with 344SQ cell lines showed that Tusc2 WT mice are more capable to degranulate compared with Tusc2 KO NK cells.

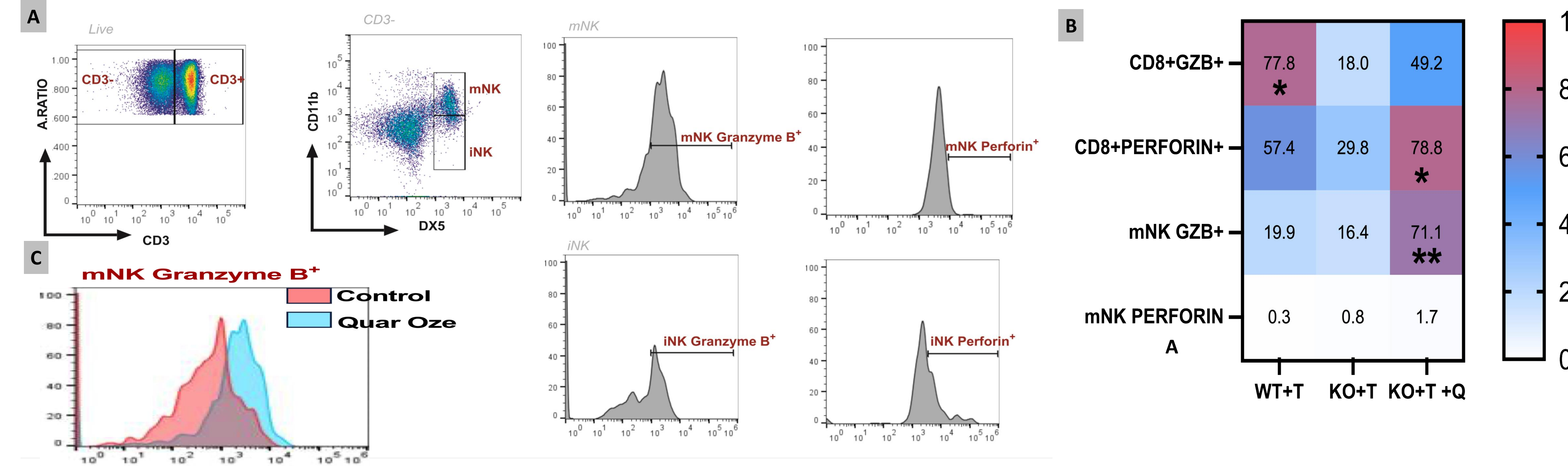


Figure 5: TUSC2 boosts cytotoxic molecules production. A. Gating strategy for NK cells from CD3⁺ populations. B. Treatment with TUSC2 lipoparticles increases the expression of Granzyme-B and perforin in cytotoxic cells. C. Representative figure for KO mice bearing a tumor, treated with Quar Oze versus control

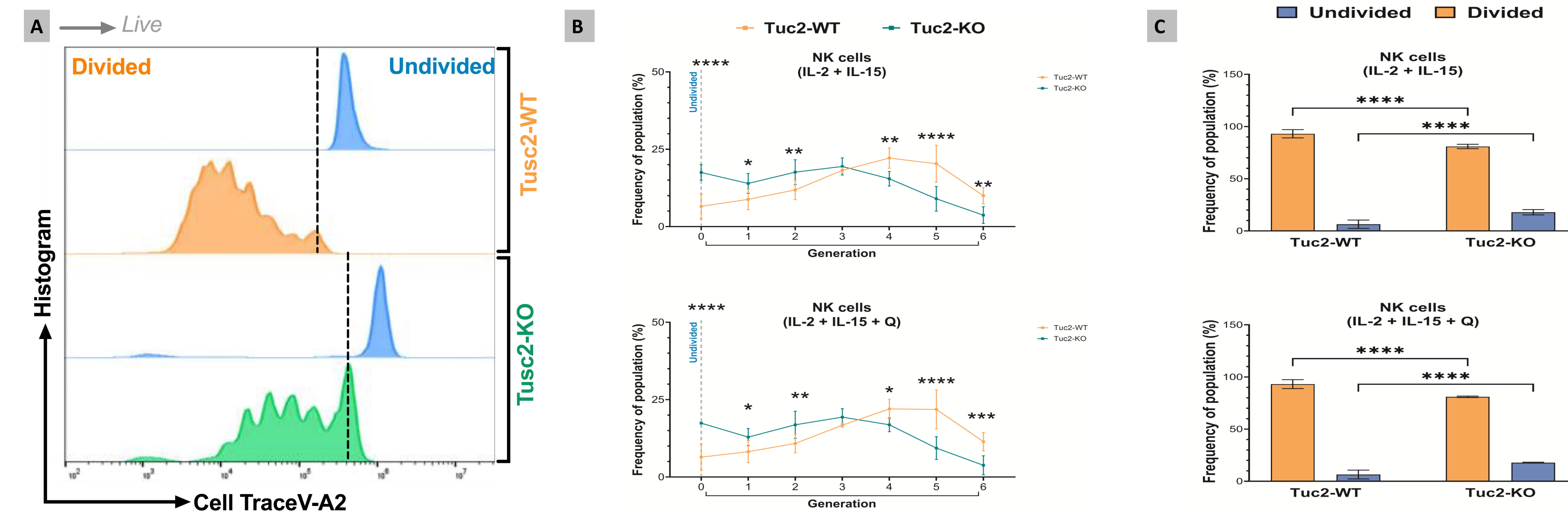


Figure 6: TUSC2 is needed for proper NK cell proliferation. A. Gating strategy for NK cells from CD3⁺ populations. B. Tusc2 KO cells failed to reach generation 6 of proliferation. C. Significant difference between Tusc2 WT NK and Tusc2 KO NK in proliferation capacity.

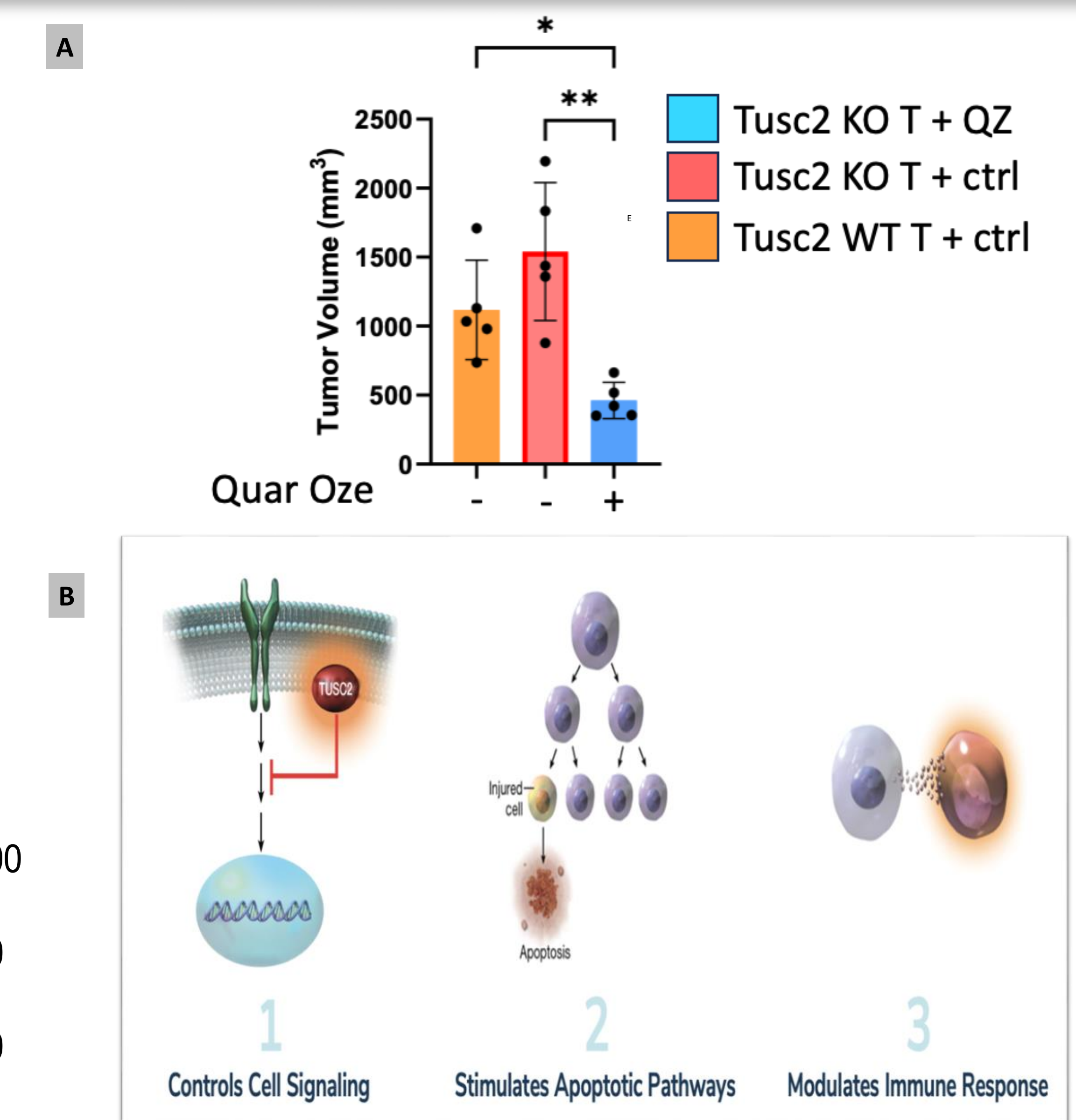


Figure 7: A. mice treated prophylactically with Quar oze showed a significant reduction in tumor volumes, however no complete elimination. B. Quar Oze, the TUSC2 lipoparticles.

Discussion

Direct cytotoxicity mediated by NK cells exerts significant anticancer effects (Chu et al, 2022). NK cells kill cancer cells directly through various mechanisms: (1) NK cells release the cytotoxic molecules, perforin and granzyme to cause apoptosis of malignant cells. (2) NK cells trigger apoptosis through the binding of membrane TNF family molecules to tumor cell membrane ligands. (3) antibody-dependent cell-mediated cytotoxicity (ADCC). (4) NK cells generate plenty of cytokines like IFN- γ that exert anti-tumor effects Meraz et al, 2018 showed earlier that the anti-tumor effect of TUSC2 was mainly attributed to NK cells.

Conclusion and Future Directions

- TUSC2 is important for cytotoxic NK cell optimal activation, which includes proliferation and production of the killing molecules
- Investigate the TUSC2-specific mechanisms of action on tumor immune cells
- Modify the injection schedule of Quar Oze to achieve a prolonged effect of the nanoparticles
- Combine nanoparticles with different immune checkpoint inhibitors to harness full function of cytotoxic cells
- RNA-seq of cytotoxic immune cells under presence and absence of TUSC2
- Run survival study to investigate durability of the response and to make sure that there is no recurrence.
- Work with TUSC2 and NK only *in vivo* study in the mice model that Rag1^{-/-} to focus on NK only effect in a biological system.
- Consider NK cell adoptive transfer after treatment with TUSC2 lipoparticles or control

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References

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