

## Improved survival in a metastatic brain tumour model with combined focused ultrasound and targeted natural killer cells

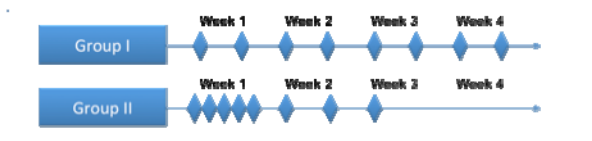
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### Problem:

Metastasis of breast cancer to the CNS is observed in up to 30% cases. Systemic treatments for breast cancer have limited success treating brain metastasis due to the blood-brain barrier (BBB) which is a significant obstacle for the pharmaceutical treatment of all brain diseases. Focused ultrasound (FUS) can temporarily and non-invasively open the BBB and has been shown to effectively deliver large therapeutic molecules into the brain. We previously demonstrated that targeted immune cells can reach the brain when combined with FUS. In the current study, we assessed the long-term effects of repeated NK-92 cell delivery with FUS on tumor growth and animal survival.

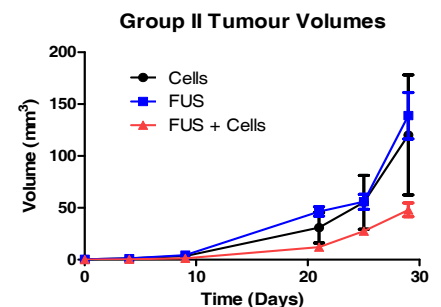
**Methods:** Two treatment paradigms were used to study the effects of FUS on targeted immune cell delivery



(Figure 1). HER2-positive human breast cancer cells were implanted in the brain of nude rats. The NK-92-scFv(FRP5)zeta cell line, which is virally transduced to express a chimeric HER2 antigen receptor, was injected into the tail vein immediately prior to sonication. A 551.5 kHz

focused transducer was used to sonicate the region of the tumour (10 ms pulses, 1 Hz pulse repetition frequency, 120 s total duration). Real-time monitoring of the acoustic emissions was used to modulate the sonication intensity. BBB opening was confirmed using contrast-enhanced 7T MR imaging. Tumour volume was tracked with serial 7T MRI and assessed post-mortem using standard histology.

**Results:** The effect of targeted NK-92 cell infusion on survival and tumour volume was enhanced with FUS. In group I, animals received 8 FUS treatments spread equally over 4 weeks. Modest increases in survival and tumour control were observed in the animals receiving FUS+NK-92 cells over controls receiving FUS alone or cells alone. In Group II, animals received 8 front-loaded FUS treatments, with 5 during the first week. Using this paradigm, significant reductions in tumour volume and survival were observed (Figure 2).



### Conclusions:

Together this data demonstrates that FUS enhances NK-92 cell translocation across the BBB. Repeated FUS and NK-92 cell treatments in a rat tumour model lead to reductions in tumour progression over time, particularly when the treatments are applied early during tumour growth. This study suggests that FUS-mediated cell delivery deserves further investigation as a potential treatment option for metastatic brain tumours.