# OFF-THE-SHELF iPSC DERIVED CAR-NK IMMUNOTHERAPY FOR SOLID TUMORS

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## BACKGROUND AND AIM

The clinical impact of Chimeric Antigen Receptor T cell (CAR-T) technologies on hematological malignancies have revolutionized cancer treatment. However, current autologous CAR-T therapies face major roadblocks for mass adoption. These include high-cost, patient-specific manufacturing, inconsistent CAR-T yield and function due to inherently depleted patient immune systems, and life-threatening adverse events. NK cell therapies have the potential to overcome at least some of these deficiencies. NK cells utilize multiple anti-cancer receptors without risk of graft versus host disease. However, they have reduced longevity *in vivo,* which may necessitate multiple infusions, increasing the risk of their rejection by the patient. Both CAR-T and CAR-NK cells are subject to checkpoint blockades and other mechanisms of immunosuppression that diminish their killer function *in vivo*.

To address these key deficiencies, we developed 'off-the-shelf', genetically-enhanced CAR-NK cells via induced pluripotent stem cells (iPSCs). Utilization of iPSCs as a renewable source for NK cells allows for consistent, precisely-defined immunotherapy and the capacity to gene-edit in multiple anti-cancer modes of action, which we have taken advantage of. The CAR-iNK cells can be cryopreserved, delivered on-demand for each patient, and crucially enable a major reduction in manufacturing cost.

## METHODS, RESULTS & CONCLUSION

Our manufacturing system is highly scalable, completely xeno- and feeder-free, yielding ~$10^5$ iNK cells from a single iPSC in less than 30 days. The iPSCs are gene-edited to carry a CAR (specific for the adenocarcinoma neoantigen TAG72) and deleted of immune suppression gene(s) to enhance NK longevity and efficacy. Unlike nearly all current allogeneic NK therapies, our iPSCs are derived from rare triple homozygous HLA donors, reducing the risk of host-mounted rejection of these iNK cells. The manufactured CAR-iNK cells display potent, on-target cytotoxic functionality against multiple ovarian cancer cell lines *in vitro* but do not kill cells from fresh healthy tissue. They are presently being evaluated *in vivo*. Our process provides a near limitless, on-demand supply of standardized 'off-the-shelf' CAR-iNK cells, with potential application to a variety of cancers, sufficient to treat many patients using a single manufactured product.