Nanoparticle-mediated mRNA delivery

COST ACTION CA 17140 – NANO2CLINIC
Working group 3 workshop
Preclinical Development of Cancer Nanomedicines: State of the Art and Future Perspectives
March 24-25th 2022, Institute of Oncology Research-IOR, Bellinzona, CH

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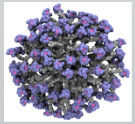

COST ACTION CA 17140
NANO2CLINIC
CANCER NANOMEDICINE - FROM THE BENCH TO THE BEDSIDE

Funded by the European Union

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ARTICLE

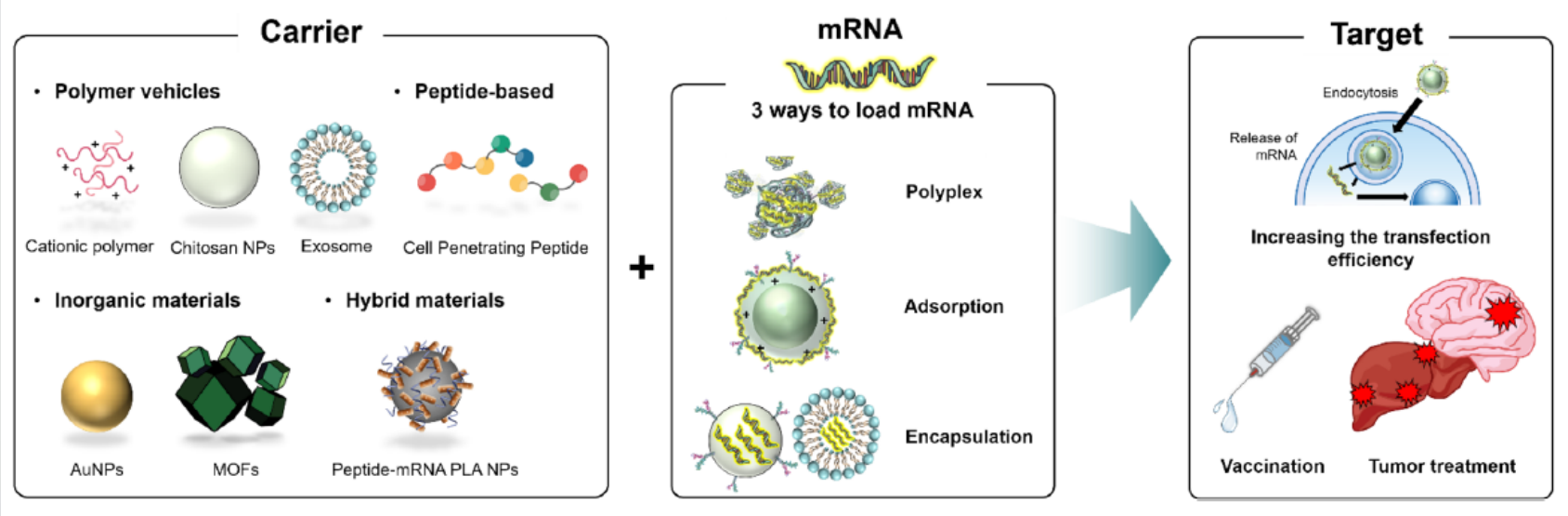
Check for updates

https://doi.org/10.1038/s41467-022-28279-8 OPEN

Combining p53 mRNA nanotherapy with immune checkpoint blockade reprograms the immune microenvironment for effective cancer therapy

Yuling Xiao[1,6], Jiang Chen[2,3,6], Hui Zhou[1,4], Xiaodong Zeng[1,4], Zhiping Ruan[2,5], Zhangya Pu[2], Xingya Jiang[1], Aya Matsui[2], Lingling Zhu[2], Zohreh Amoozgar[2], Dean Shuailin Chen[1], Xiangfei Han[1], Dan G. Duda[2,7]✉ & Jinjun Shi[1,7]✉

mRNA-based therapeutics



https://doi.org/10.1007/s13206-022-00052-5

Genetic materials should reach the targeted site efficiently and safely

- Carriers should protect the cargo from *in vivo* environments
- Induce efficient transfection into cells
- Produce high levels of specific proteins

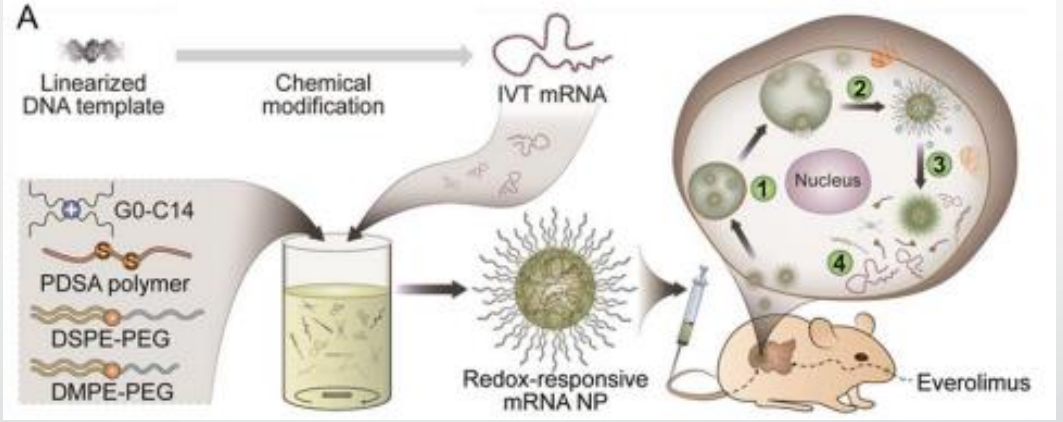
Cancer treatment

Applications require

- Protein expression for limited duration
- High carrier stability
- Moderate binding force
- Efficient cellular uptake
- Endosomal escape

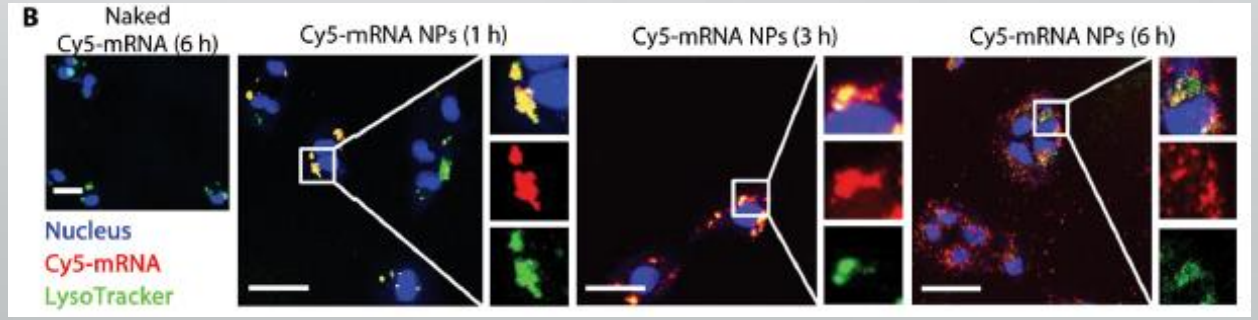
Synthetic mRNA nanoparticle-mediated restoration of p53

- *In vitro* transcription to synthesize EGFP mRNA and *p53*-mRNA
- Self-assembly approach to engineer lipid-polymer hybrid NPs for effective loading of the chemically modified mRNA



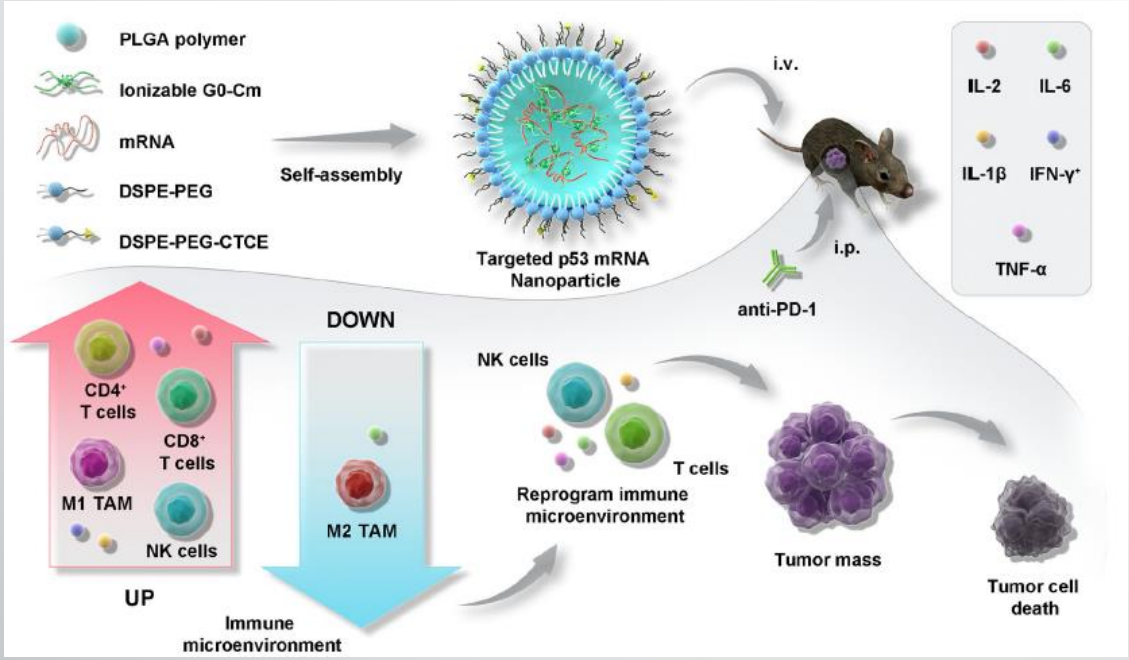
- Ionizable lipid-like compound Go-C14 for mRNA complexation
- Biocompatible poly(lactic-co-glycolic acid) polymer for forming a stable NP core to carry the Go-C14/mRNA complexes
- Lipid-poly(ethylene glycol) layer for stability and high tumor cell uptake

- Cytosolic delivery of mRNA using engineered NPs *in vitro*

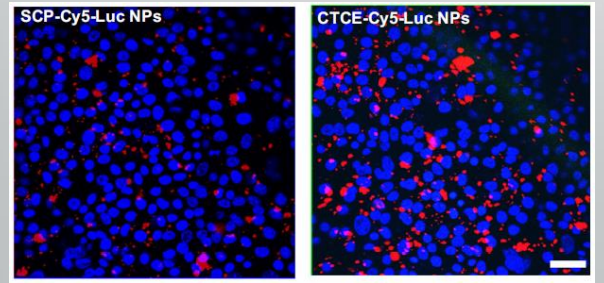


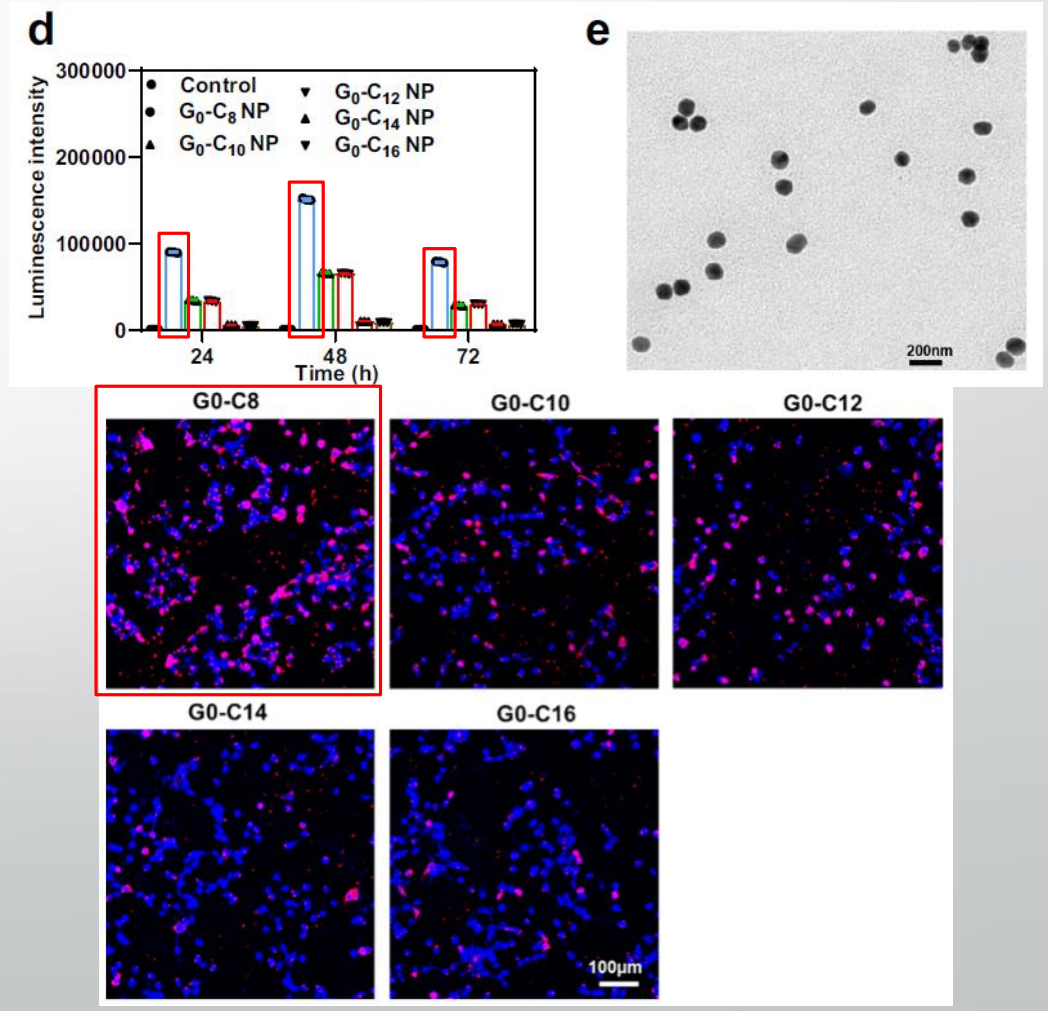
https://doi.org/10.1126/scitranslmed.aaw1565

Combining p53 mRNA nanotherapy with immune checkpoint blockade



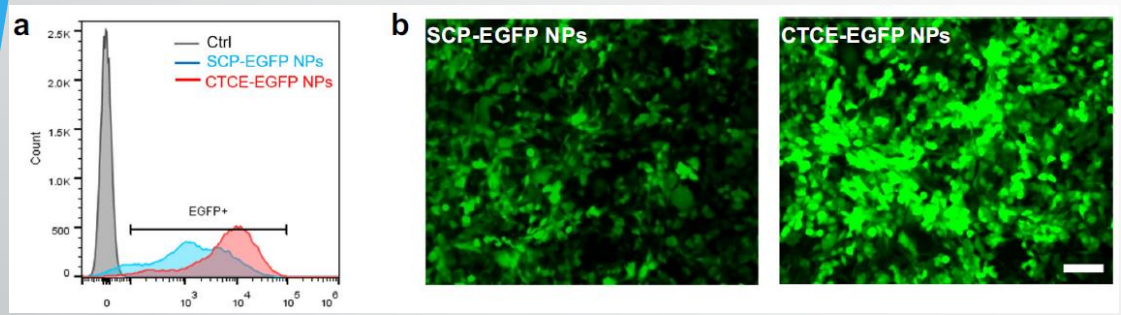
Engineered the hybrid NPs for selective hepatocellular carcinoma (HCC) targeting and high mRNA transfection efficiency, by modifying the NPs with the targeting peptide CTCE (specific to CXCR4).

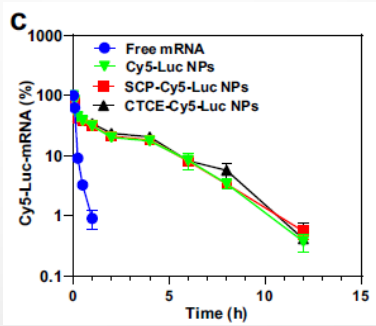


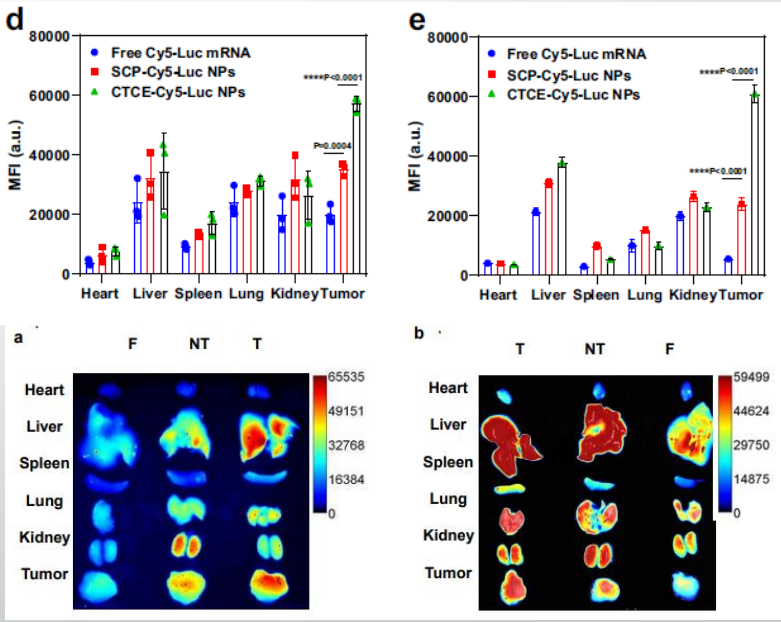


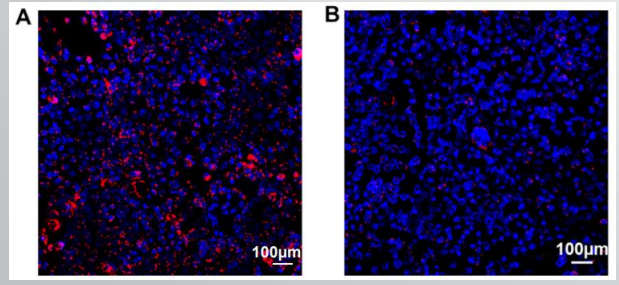
Combining p53 mRNA nanotherapy with immune checkpoint blockade

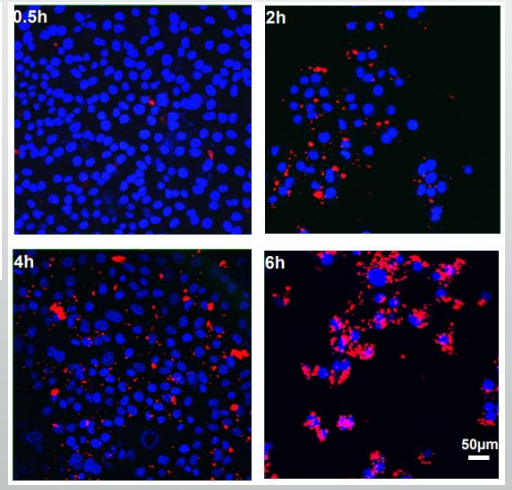
CTCE-targeted NPs demonstrated significantly enhanced cellular uptake, mRNA transfection efficiency, and intratumoral accumulation





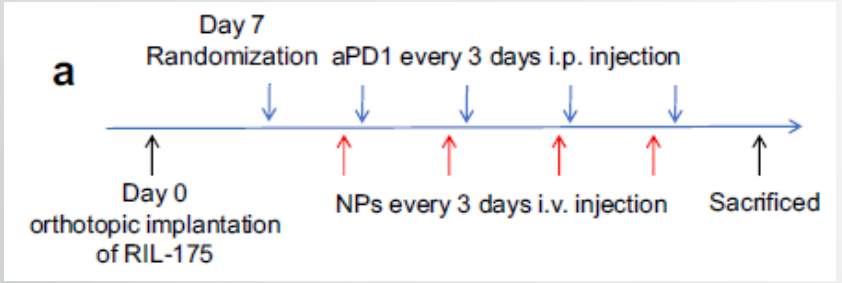


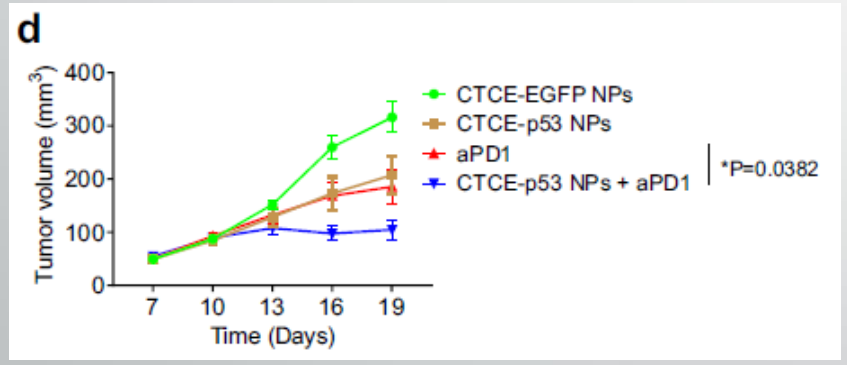


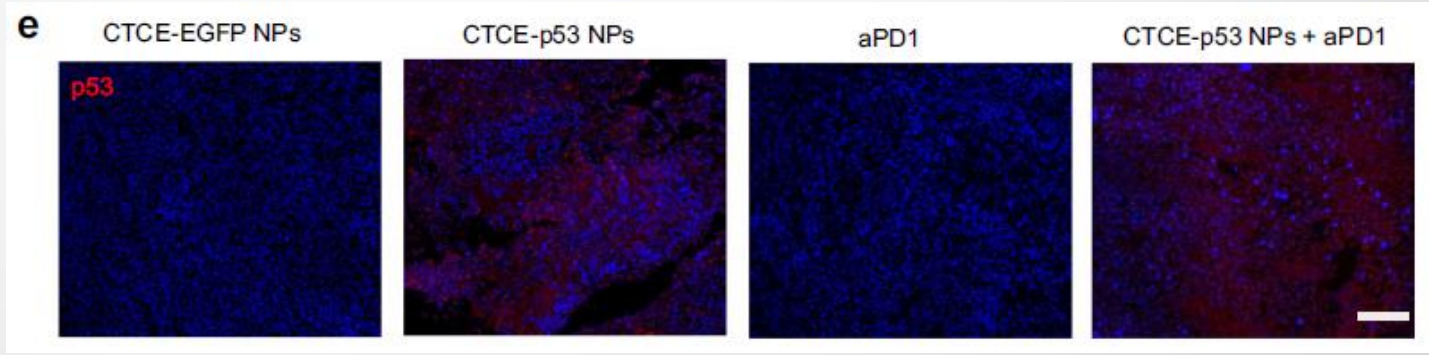


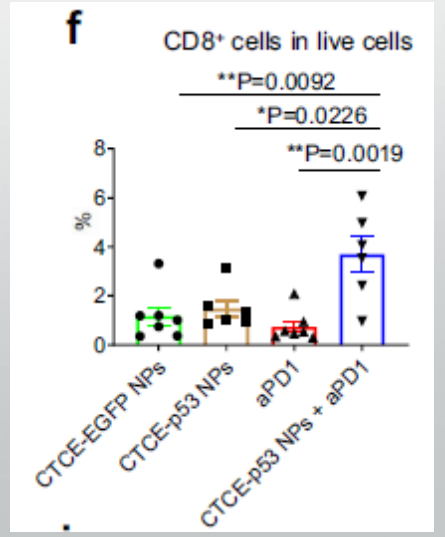
Combining p53 mRNA nanotherapy with immune checkpoint blockade

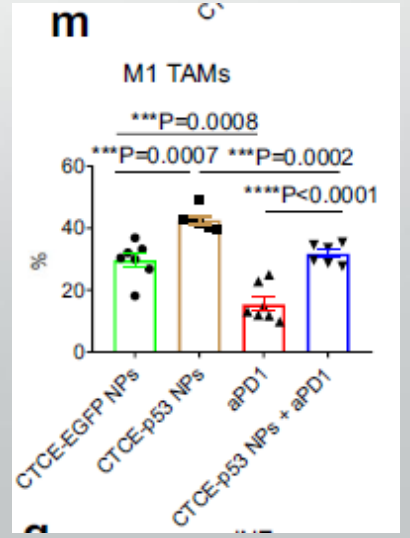
The combination of CTCE-p53 NPs and PD-1 blockade effectively and globally reprogrammed the immune TME of HCC by increasing effector immune cells and cytokine levels in the tumor

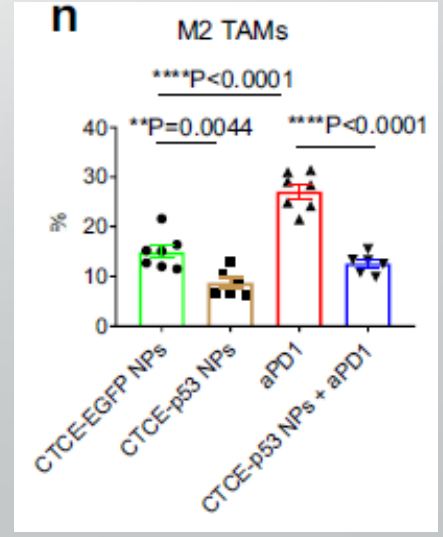






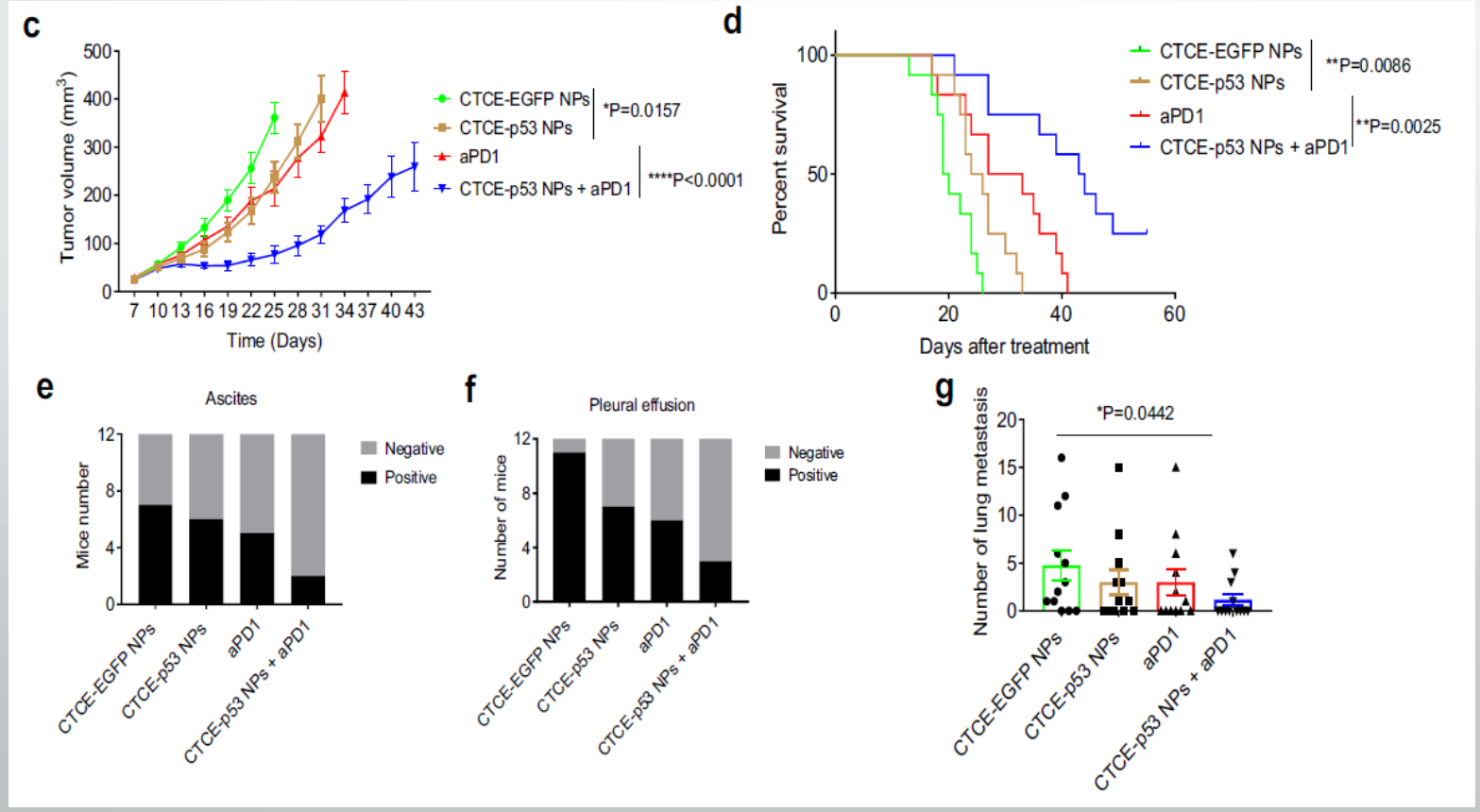






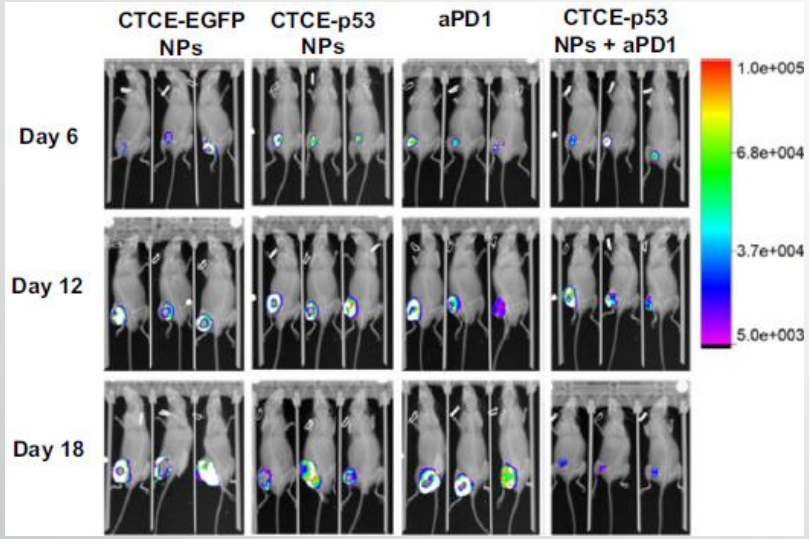
Combining p53 mRNA nanotherapy with immune checkpoint blockade

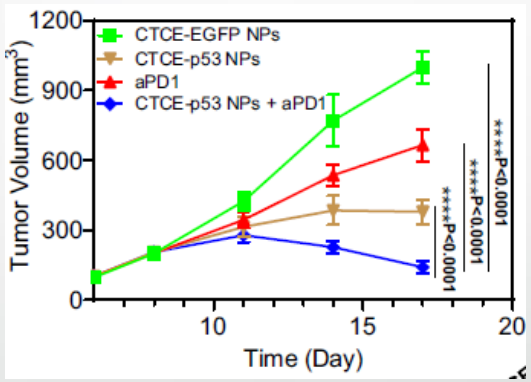
p53 restoration using CXCR4-targeted mRNA NPs can markedly improve the efficacy of aPD1 therapy in p53 deficient HCC

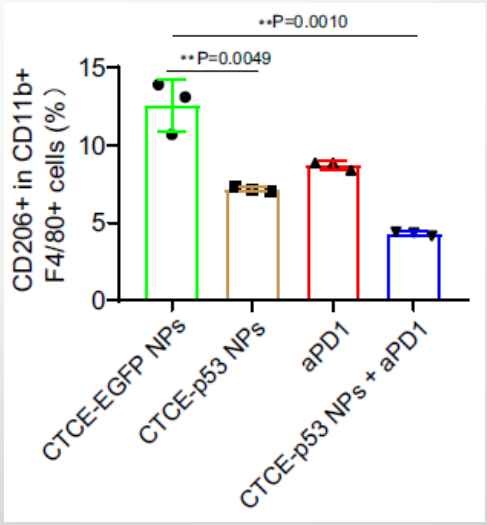


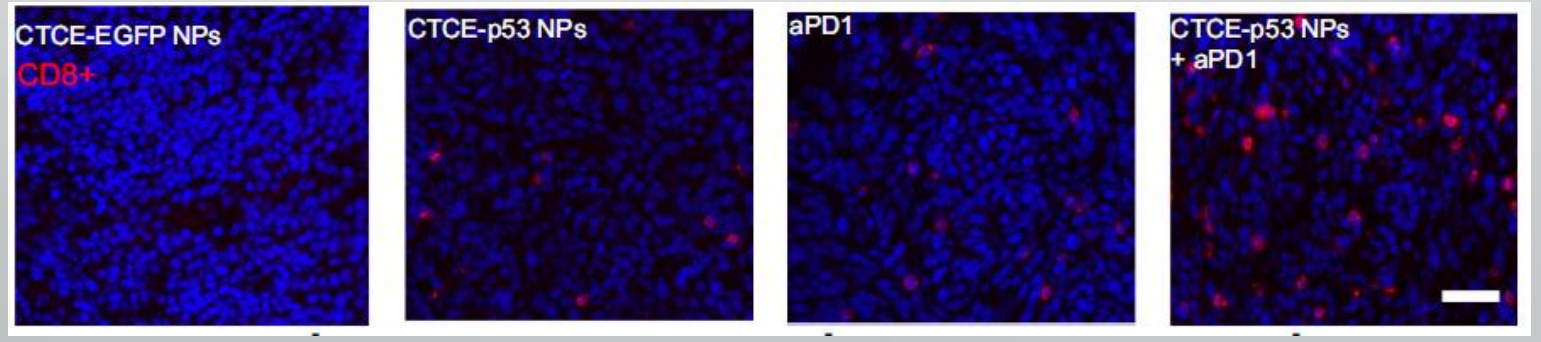
Combining p53 mRNA nanotherapy with immune checkpoint blockade

Targeting HCC cells with CTCE-p53 NPs combined with aPD1 therapy triggers anti-tumor immunity and reprograms the immune TME of HCC both in the liver and other organs







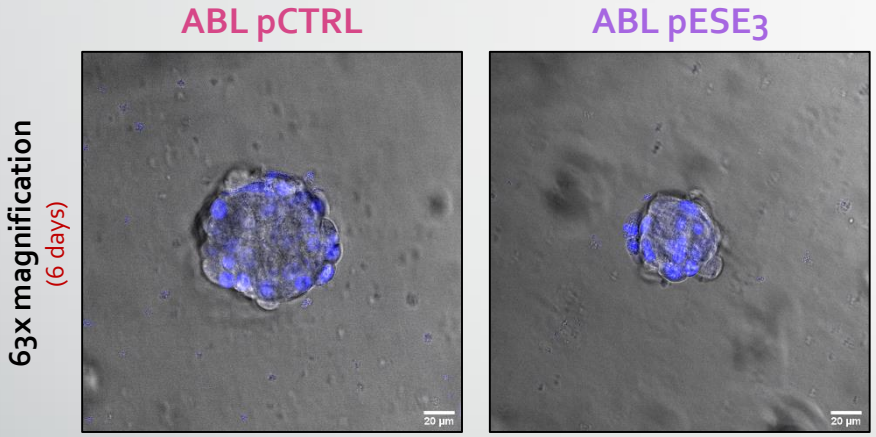


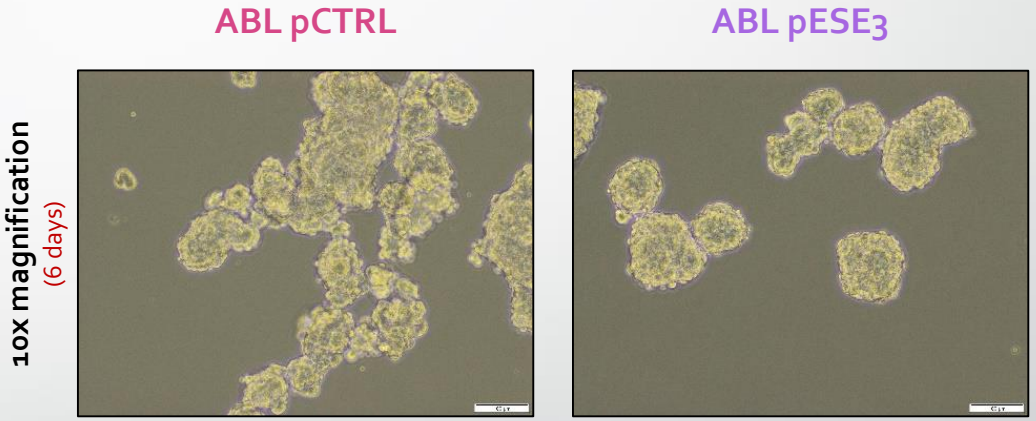
Combining p53 mRNA nanotherapy with immune checkpoint blockade

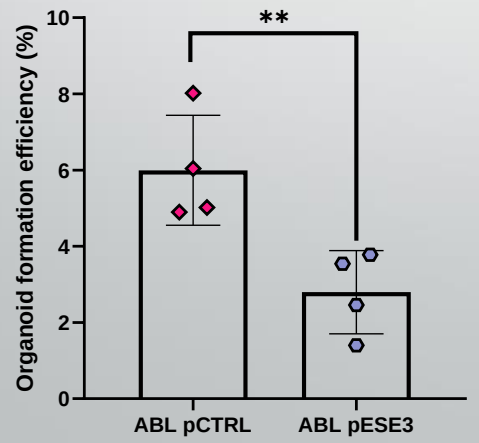
- Effective p53 restoration was achieved by developing a CXCR4-targeted mRNA NP platform
- Optimization in the use of ionizable lipid-like compounds and the densities of CXCR4-targeting ligands improved mRNA translation and HCC targeting *in vivo*
- The combination of CXCR4-targeted p53 mRNA NPs with aPD1 led to a potent anti-tumor effect in intrahepatic and ectopic models of HCC with p53 loss
- The combination treatment effectively reprogrammed the immune TME

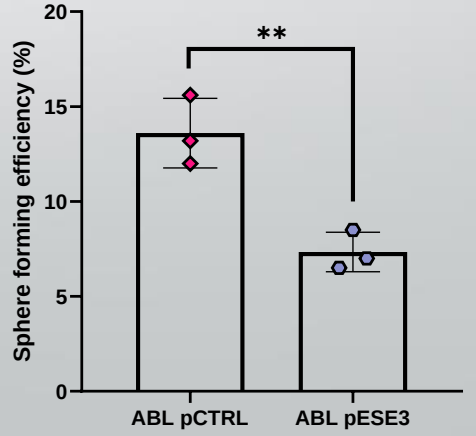
Potential applications

Re-expression of the tumor suppressor ESE3/EHF in aggressive prostate cancer cells reverses the malignant phenotype









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