



CRS 2022 Annual Meeting & Expo

Advanced Delivery Science

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mRNA Nanomedicine for Precision Cancer Immunotherapy

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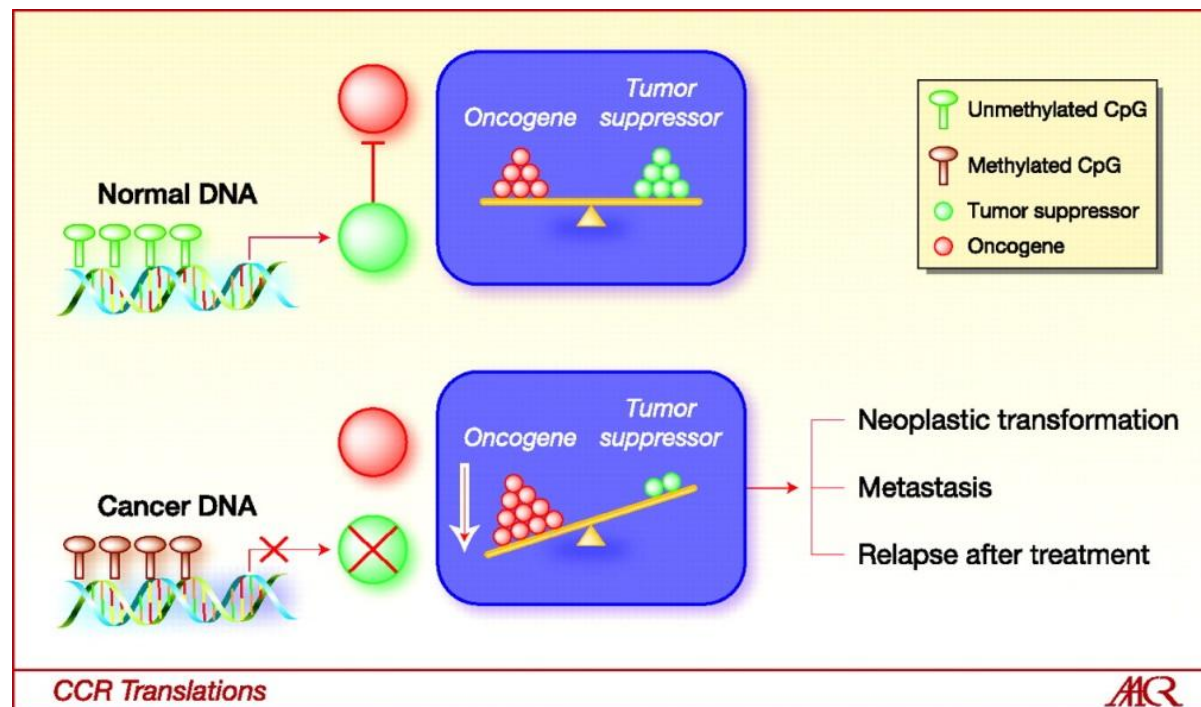
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL



Mass General Brigham



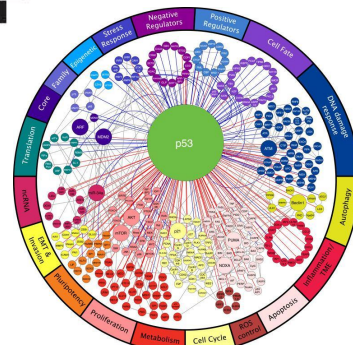
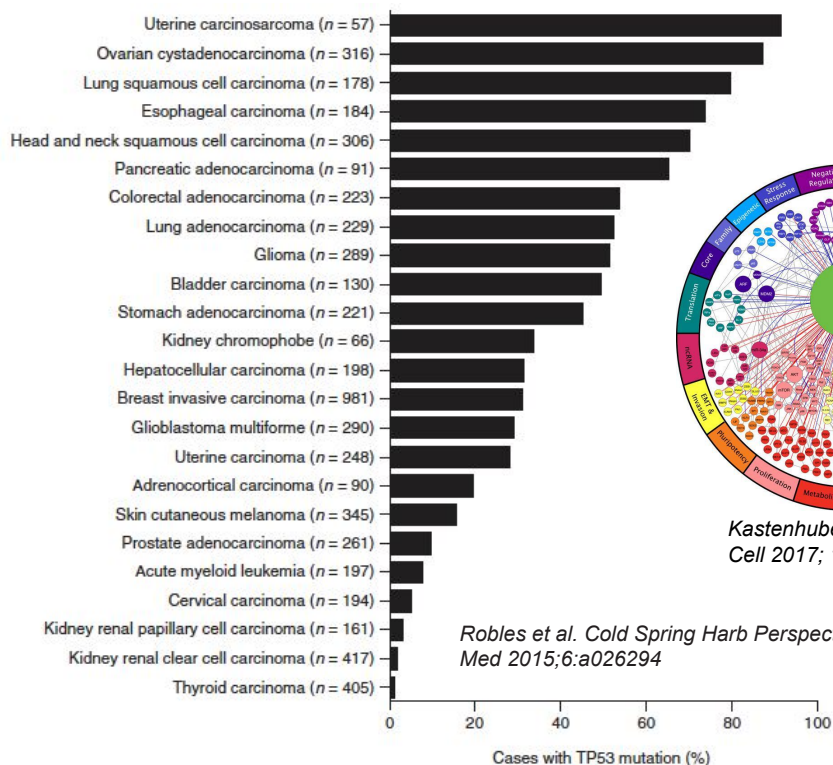
Genetic Causes of Cancer



- ❖ Pro-tumorigenic drivers: many are considered 'difficult-to-drug'
- ❖ Tumor suppressors: deleted or mutated

Opportunities for RNA medicines

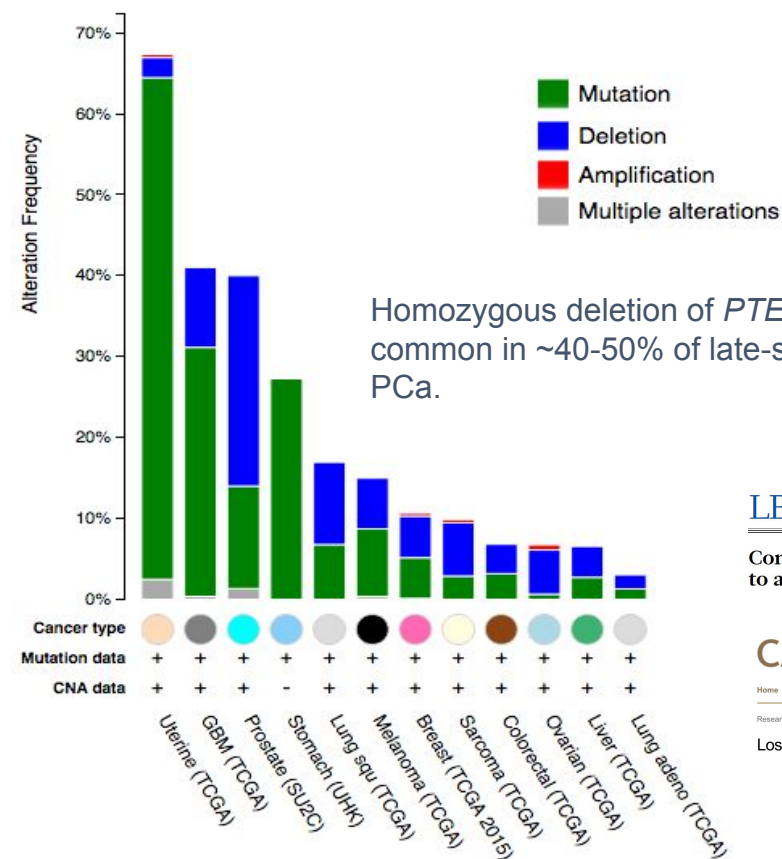
p53



Kastnerhuber and Lowe,
Cell 2017; 170:1062

Robles et al. Cold Spring Harb Perspect
Med 2015;6:a026294

PTEN



LETTER

Nature

doi:10.1038/nature12948

Convergent loss of *PTEN* leads to clinical resistance to a PI(3)K α inhibitor

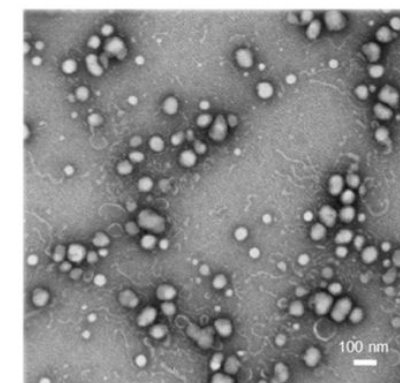
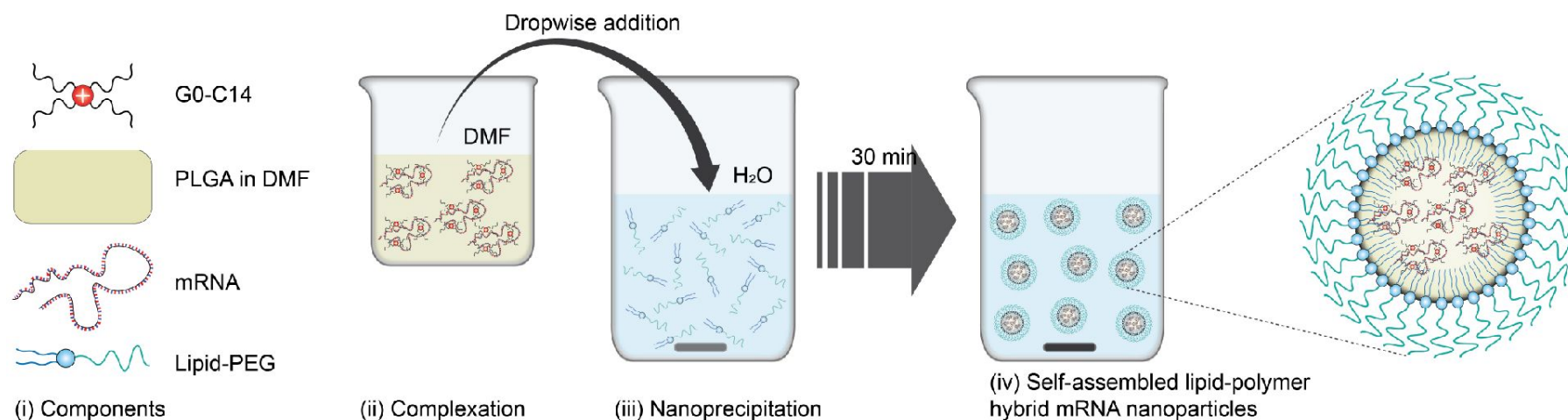
CANCER DISCOVERY

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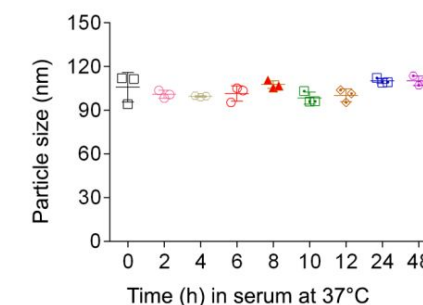
Research Articles

Loss of *PTEN* Promotes Resistance to T Cell-Mediated Immunotherapy

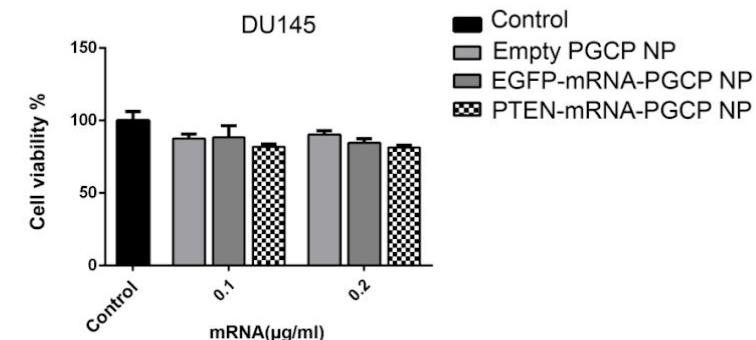
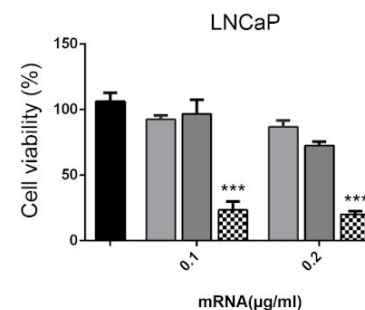
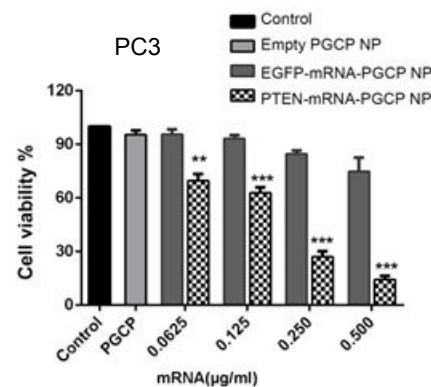
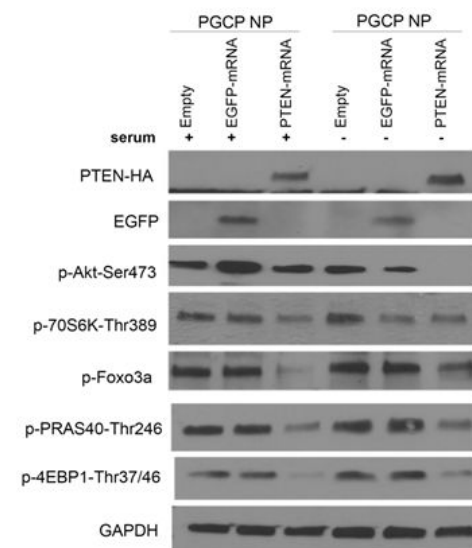
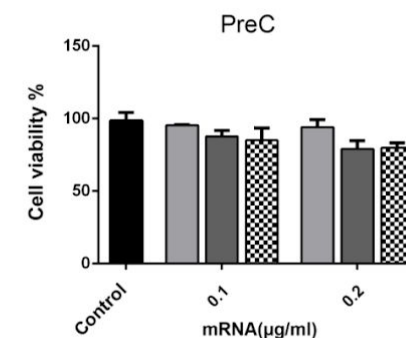
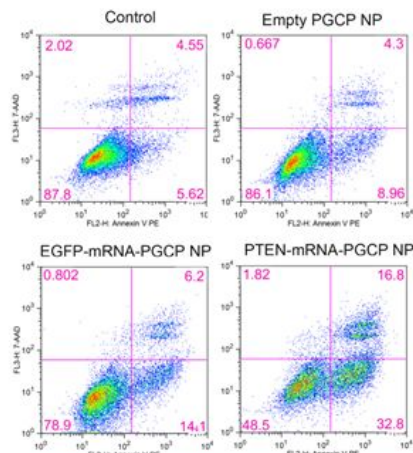
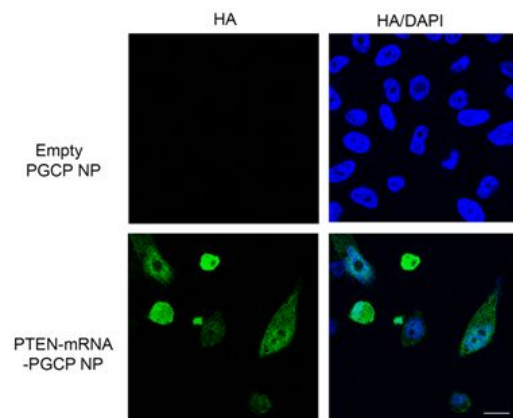
Lipid-Polymer Hybrid mRNA NP Formulation



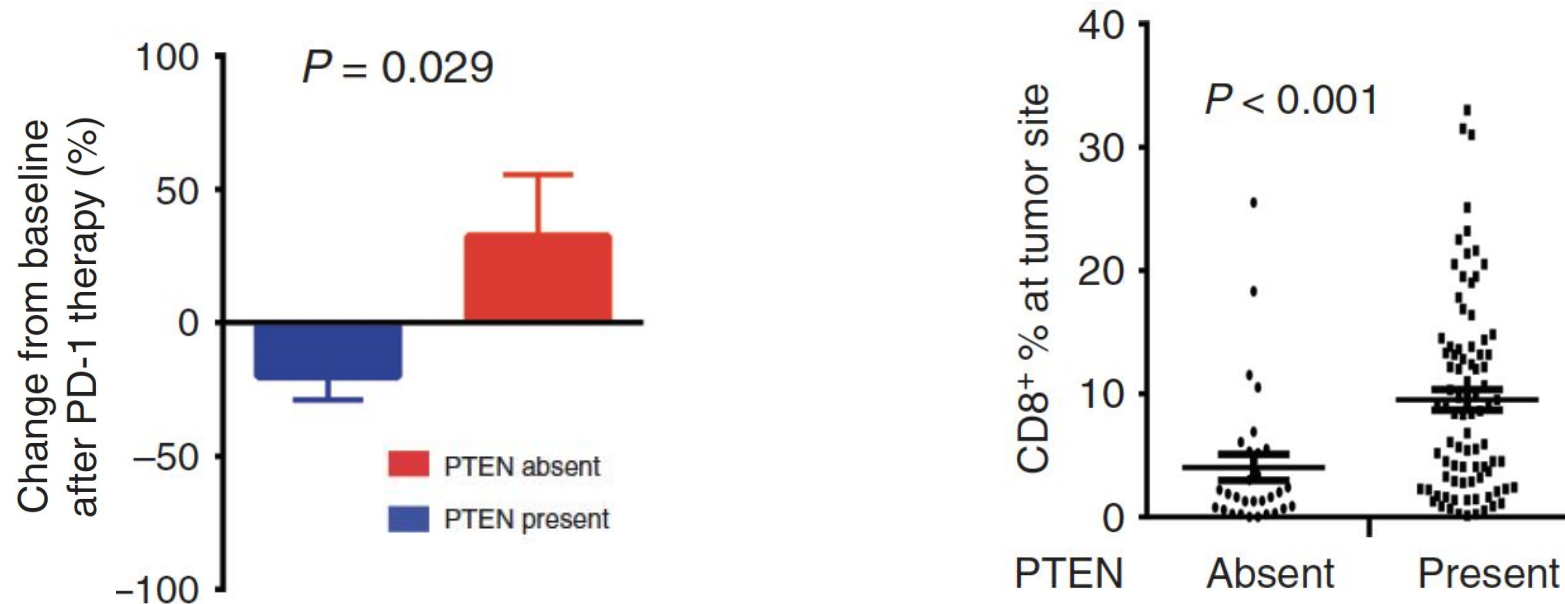
- Enhance cellular uptake and endosomal escape
- Prolong systemic circulation and improve tumor accumulation



PTEN Restoration for Treatment of *PTEN*-null Human PCa



Loss/Mutation of PTEN Is Correlated with Poor Immunotherapy

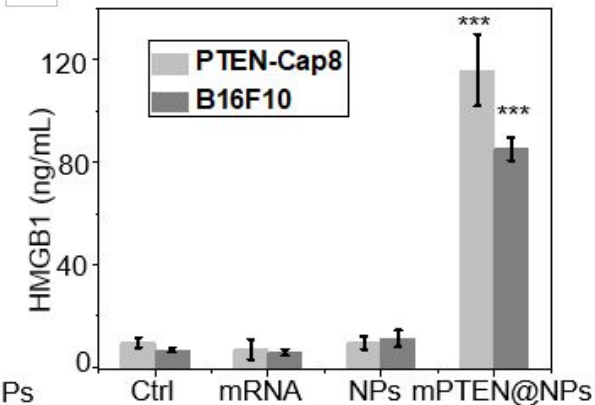
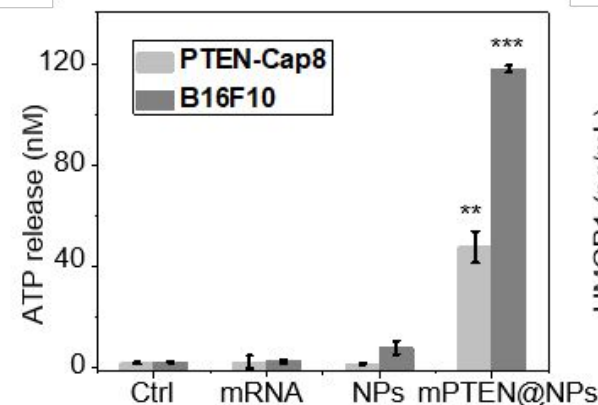
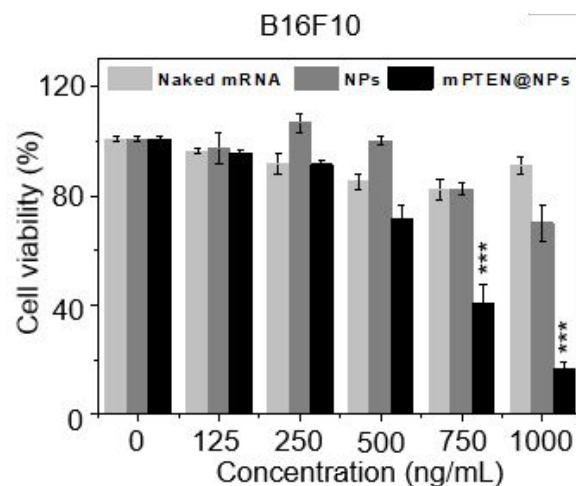
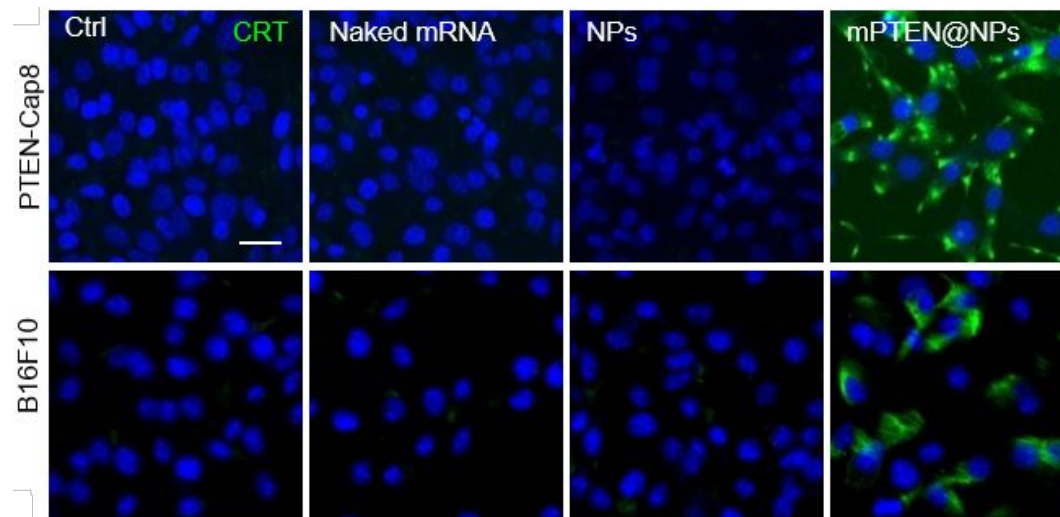
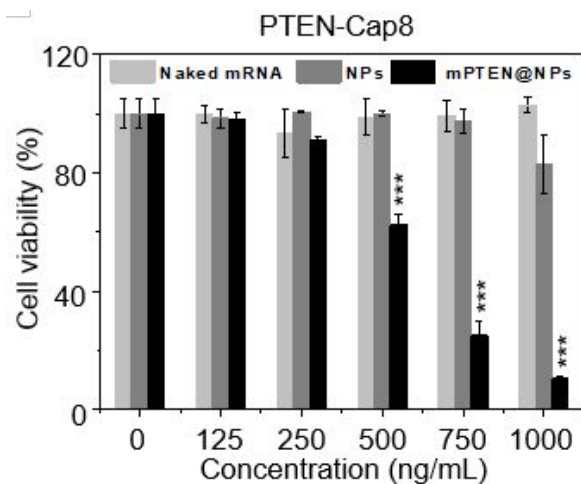


Hwu lab, Cancer Discov 2015; Futreal lab, Sci Transl Med 2017; Van Allen lab, Immunity 2017; Tolaney lab, Clin Cancer Res 2020

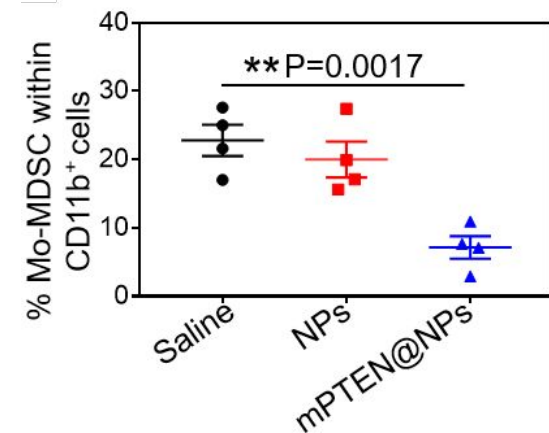
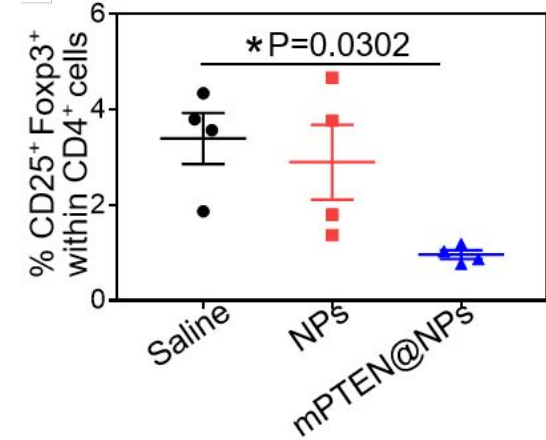
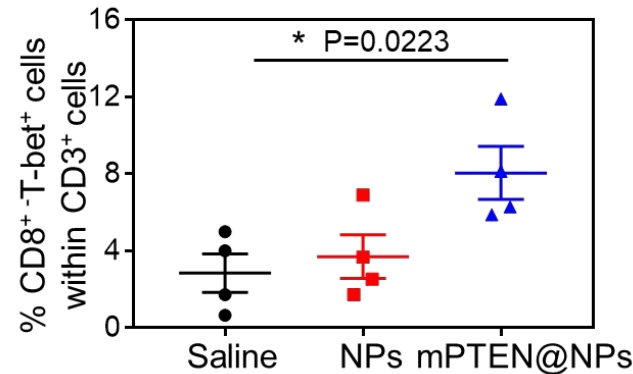
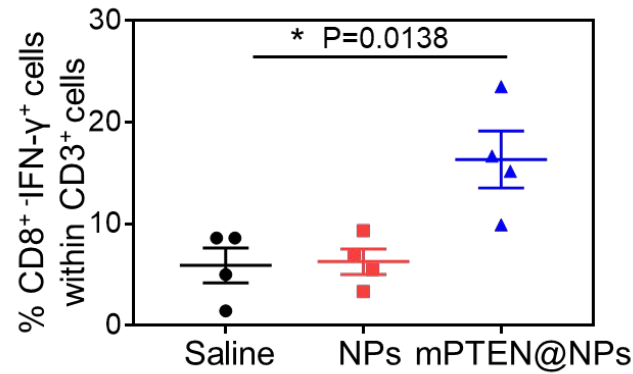
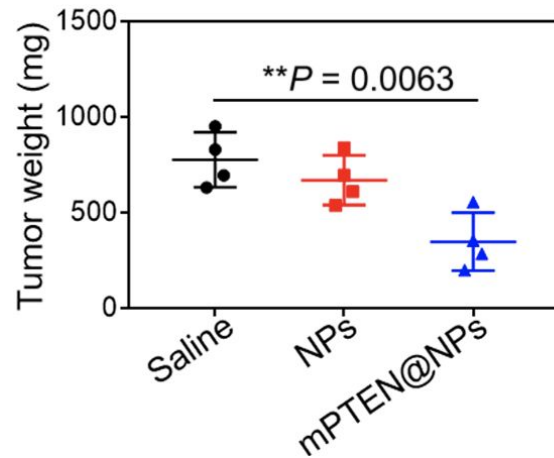
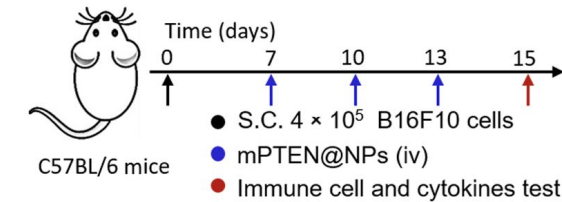
PTEN loss is associated with

- i) decreased T-cell infiltration at tumor sites*
- ii) increased expression of immunosuppressive cytokines*
- iii) poor-response or resistance to immune checkpoint blockade (e.g., anti-PD-1)*

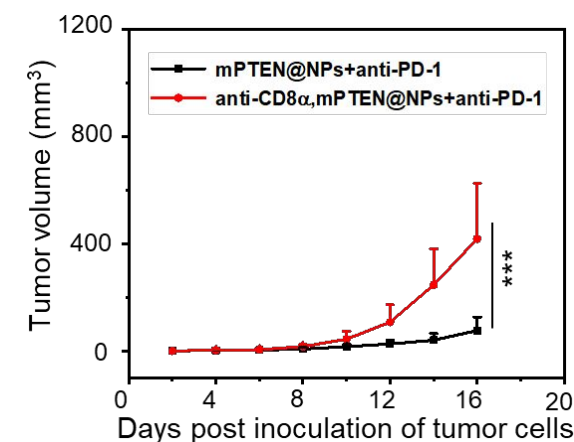
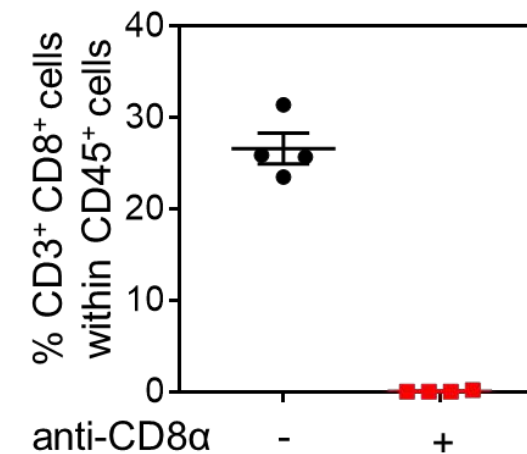
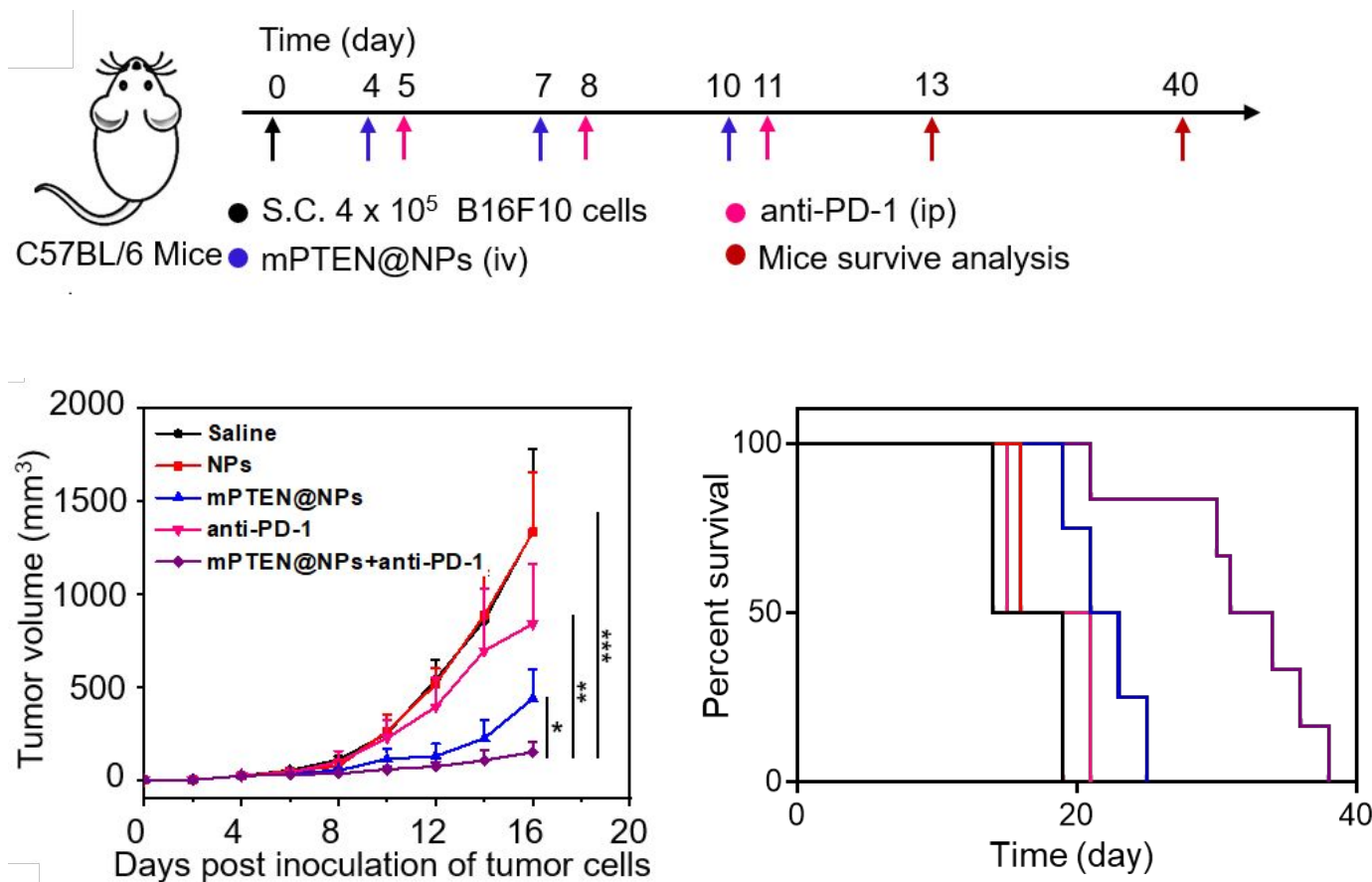
PTEN Restoration Induces Immunogenic Cell Death (ICD)



PTEN Restoration Modulates the Immunosuppressive Tumor Microenvironment

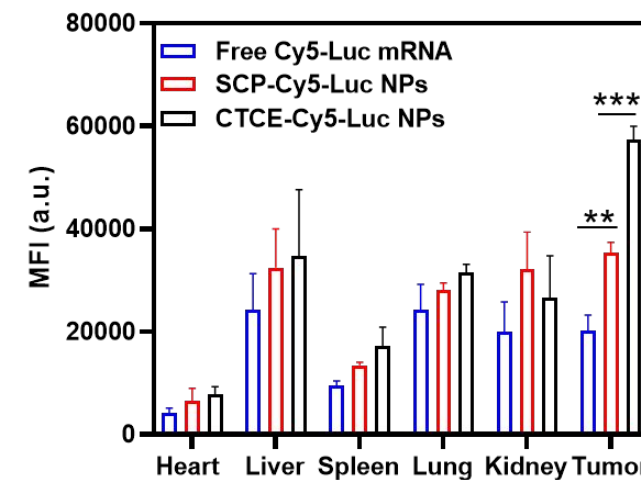
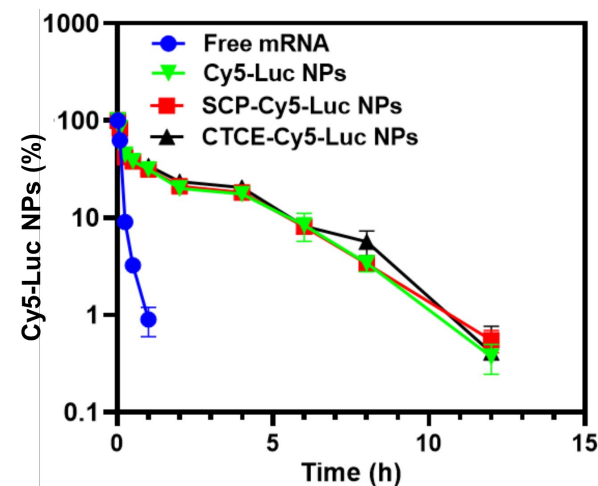
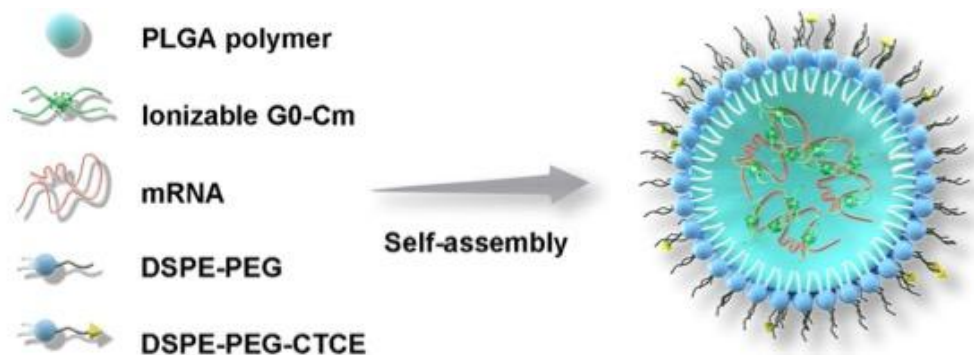


PTEN mRNA NPs Improves anti-PD-1 Efficacy in s.c. Melanoma Model

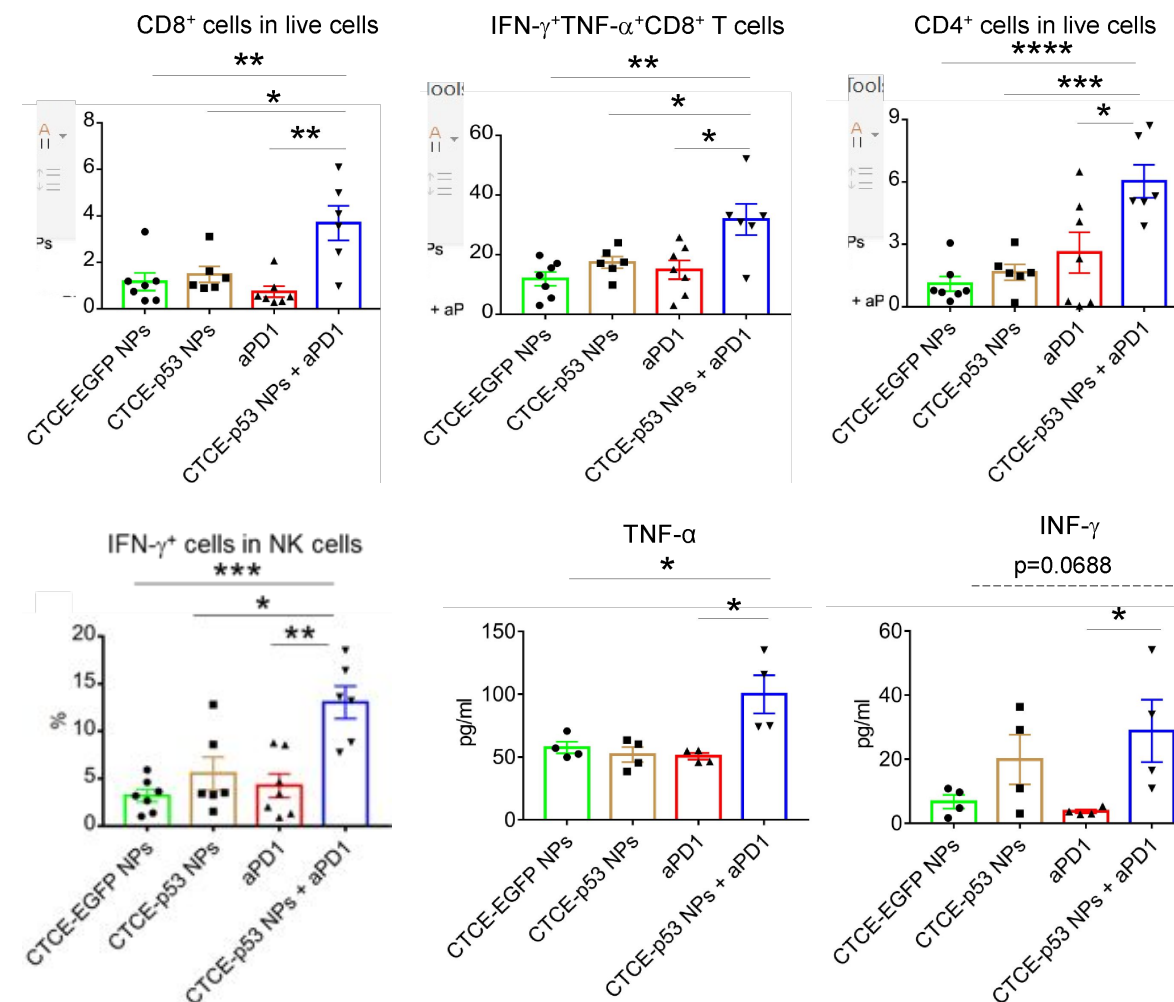
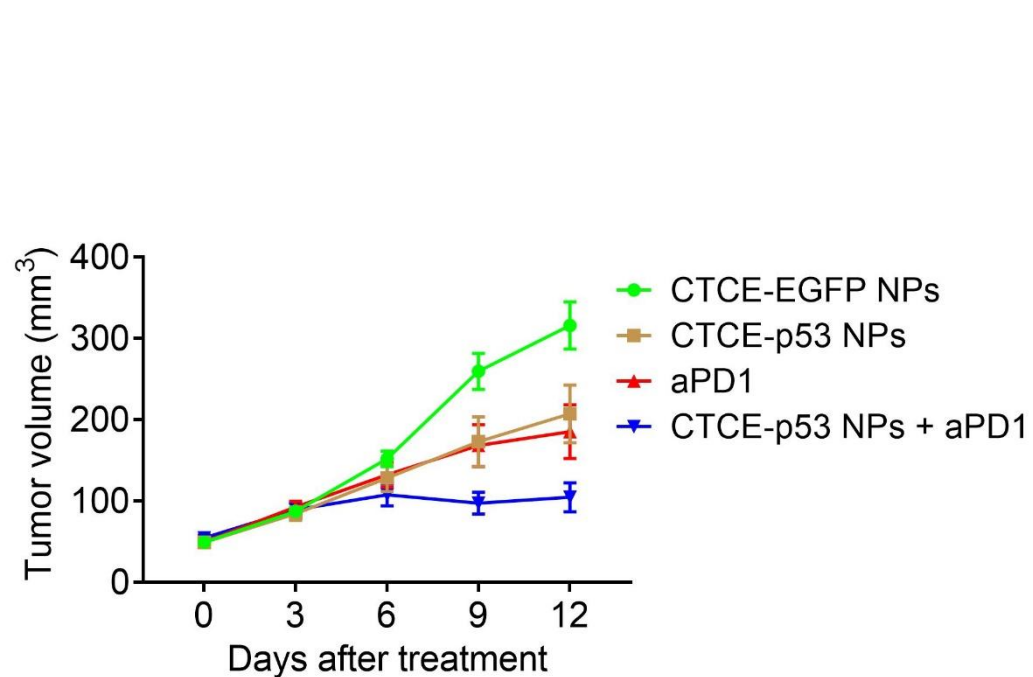


Combination of p53 Restoration and ICB for HCC

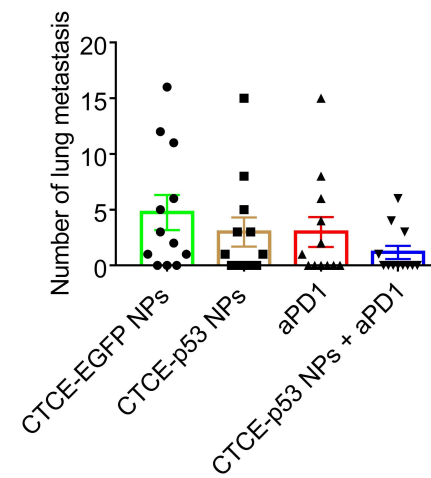
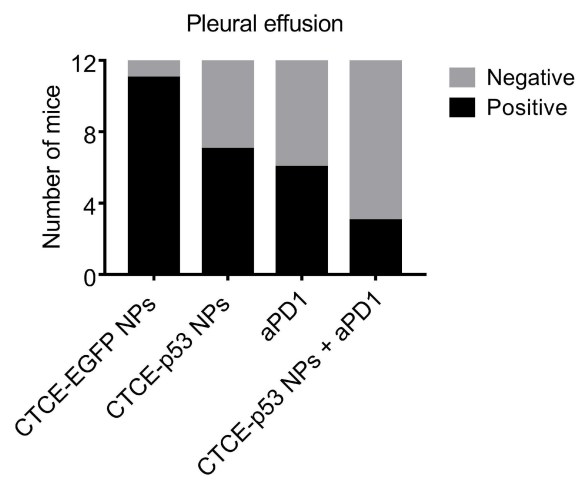
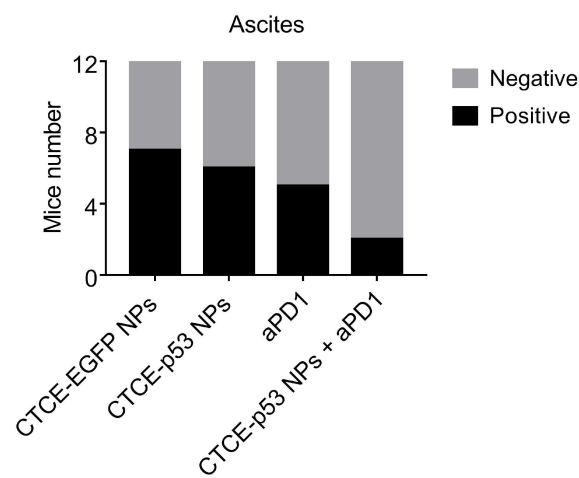
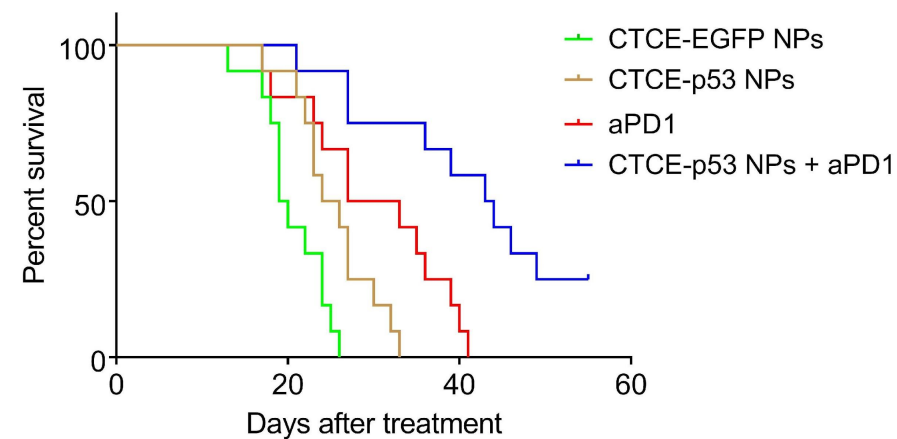
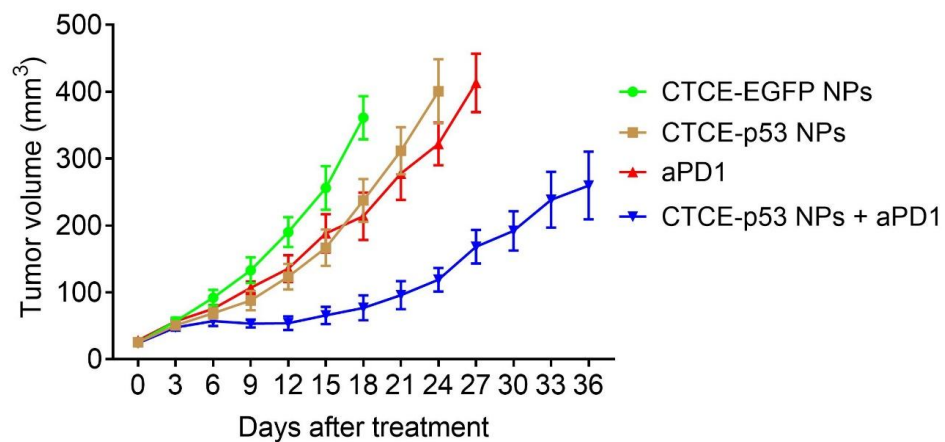
- Anti-PD-L1 with anti-VEGF: first-line standard of care treatment for HCC
- Anti-PD-1 with anti-CTLA4: second-line for HCC



Combinatorial Treatment Reprograms the Immune Microenvironment



Synergistic Anti-Tumor Efficacy in HCC



Summary

- The lipid-polymer hybrid NPs were developed for systemic mRNA delivery to restore tumor suppressors (PTEN and p53).
- Restoration of PTEN induced anti-tumor immunity and improved the efficacy of immune checkpoint inhibitors (anti-PD-1).
- *Combination of p53 immune checkpoint inhibitors reprograms immune microenvironment for better HCC treatment.*
- The combination of p53 restoration and mTOR inhibition led to potent anti-tumor effect in p53-deficient HCC and NSCLC (*Sci Transl Med* 2019).
- *The NP co-delivery of mRNA antigen and TLR7/8 adjuvant elicits strong anti-tumor immunity (Biomaterials 2021).*

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