Introduction: Platinum-based drug resistance is intricately associated with a disordered tumor metabolic-immune microenvironment (TMIME). This study sought to develop a combined strategy for TMIME reprogramming to enhance cisplatin sensitivity.

Methods: A gene-chemo co-delivery nanoparticle (NP) was engineered using poly(β-amino ester) (PBAE) to encapsulate a cisplatin prodrug (Pt^{IV}) and a CRISPR/Cas9-PKM2 plasmid via self-assembly. The morphology and elemental composition of $PPPt^{IV}$ NPs were visualized using transmission electron microscope (TEM) and field emission TEM. The hydrodynamic size, polydispersity index, and zeta potential were measured using dynamic light scattering. The viabilities and apoptosis effects were investigated in SCC7 and Cal27 cells treated with NPs using CCK-8 and Annexin V/PI double staining assays. The in vivo biodistribution and antitumor efficacy were investigated in SCC7 tumor-bearing C57BL/6 mice.

Results: $PPPt^{IV}$ NPs exhibited a uniform near-spherical morphology with a positively charged surface and an average diameter of approximately 150 nm. $PPPt^{IV}$ NPs possessed good stability and pH-responsive release. Mechanically, $PPPt^{IV}$ NPs were efficiently internalized through endocytosis, then escaping from lysosomes and releasing their components. Pt^{IV} was reduced to cisplatin (Pt^{II}) via GSH depletion, leading to increased DNA damage and ROS levels to induce apoptosis. CRISPR/Cas9-mediated PKM2 knockdown significantly reduced lactic acid production via inhibiting the Warburg effect, while downregulating PD-L1 and HIF-1α levels. These metabolic alterations remodel tumor immune microenvironment by promoting dendritic cell maturation, polarizing macrophages to the M1 phenotype, and modulating the cytokine release (IFN-γ, TNF-α, IL-12, and IL-10), thereby initiating T cell-mediated antitumor immunity. As a result, $PPPt^{IV}$ NPs realized the chemo-immunotherapy goal. Compared to cisplatin alone, $PPPt^{IV}$ NPs achieved superior antitumor efficacy against both in situ and recurrent tumors with less nephrotoxicity in vivo.

Conclusions: The combined chemo-immunotherapy nanohybrids address the limitations of cisplatin, including resistance and adverse effects, and demonstrate significant potential for clinical application in patients resistant to cisplatin.