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# Dendritic Nanoparticles for Effective Immune Checkpoint Inhibition

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## Extended Abstract

Dendritic polymers, particularly poly(amidoamine) (PAMAM) dendrimers, have garnered significant attention as drug delivery platforms for various therapeutic agents over the past few decades[1]. These macromolecules offer several advantages, including: (i) the ability to mediate strong multivalent binding interactions, (ii) efficient, controlled tumor penetration due to their sub-10 nm size and deformability, and (iii) facile multifunctionalization through diverse conjugation chemistries. In this presentation, we highlight our recent efforts using surface-engineered PAMAM dendrimers for cancer immunotherapy[2, 3]. Specifically, immune checkpoint inhibitors (ICIs), either in a form of antibodies or engineered peptides targeting programmed death-ligand 1 (PD-L1) on tumor cells, were conjugated to a generation 7 (G7) PAMAM dendrimer. We performed comprehensive characterization of the conjugates, including binding kinetics measurements, in vitro cell assays, and in vivo biodistribution and efficacy studies. Three independent binding assays—surface plasmon resonance (SPR), bio-layer interferometry (BLI), and atomic force microscopy (AFM)—revealed that the dendrimer-ICI conjugates exhibited binding kinetics up to five orders of magnitude greater than the corresponding free ICIs. This enhancement is likely attributed to the multivalent binding effect facilitated by the dendrimer's structure, along with stabilization of the peptide's folded conformation. The improved binding kinetics translated into significantly enhanced immunotherapeutic efficacy and in vivo response, as demonstrated in a syngeneic mouse model. Additionally, the plasma half-life and tumor-selective accumulation of the dendrimer-ICI conjugates were both substantially increased, suggesting that this platform is particularly beneficial for peptide-based ICIs. Our findings demonstrate the potential of dendrimer-based conjugates to significantly enhance the therapeutic efficacy of immunotherapeutic agents, providing a novel platform technology for virtually any ICI.

## References

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