Intratumoral pH-Activated Nanocytokine Boosts Immunotherapy to Eradicate Cold Tumors

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A strategy for potentiating antitumor immunity is highly demanded to improve the response rate of cancer immunotherapies, especially for immunologically cold tumors. Interleukin-12 (IL-12) is a strong inflammatory cytokine with great potential for enhancing antitumor immunity[1]. However, systemic IL-12 shows intolerable immune-related adverse events (irAEs)[2], calling for approaches to reduce off-target exposure and enhance intratumoral activation. Here, we propose a strategy called "Nanocytokine" by loading IL-12 protein into a polymeric micelle that can sense the intratumoral pH to selectively unleash IL-12 activity inside tumors.

The Nanocytokine is formulated using carboxydimethylmaleic anhydride (CDM)-functionalized poly(ethylene glycol)-poly(L-Lysine) (PEG-pLL) block copolymer. Mixing the polymer with IL-12 protein leads to the assembly of polymeric micelles with a 40 nm diameter, called "IL-12-based Nanocytokine (Nano-IL-12)" (***Figure 1***). Nano-IL-12 can selectively dissociate in an intratumoral acidic environment (pH 6.5) and release IL-12 to agonize antitumor immunity. Upon systemic injection, Nano-IL-12 prolongs blood circulation and restricts IL-12 activity in healthy tissues, reducing the systemic immune activation associated with toxicity and counteractive responses. Meanwhile, Nano-IL-12 shows enhanced accumulation and high activation rate in tumors. This enhanced and localized intratumoral activation of Nano-IL-12 induces profound gene and cellular changes in the tumor microenvironment, leading to boosted intratumoral inflammation and elevated infiltration of effector immune cells. At a 500 μg/kg IL-12 equivalence dose with multiple injections, Nano-IL-12 shows satisfactory therapeutic effects against murine melanoma and both primary and metastatic triple negative breast cancer (TNBC) models. The combination of Nano-IL-12 with checkpoint inhibitors further enhances the therapeutic response and eradicates tumors. Especially in the metastatic TNBC model, the combination therapy of Nano-IL-12 with checkpoint inhibitors induces a complete response in all mice, with robust immune memory confirmed by the effective tumor rejection after a rechallenge with cancer cells.

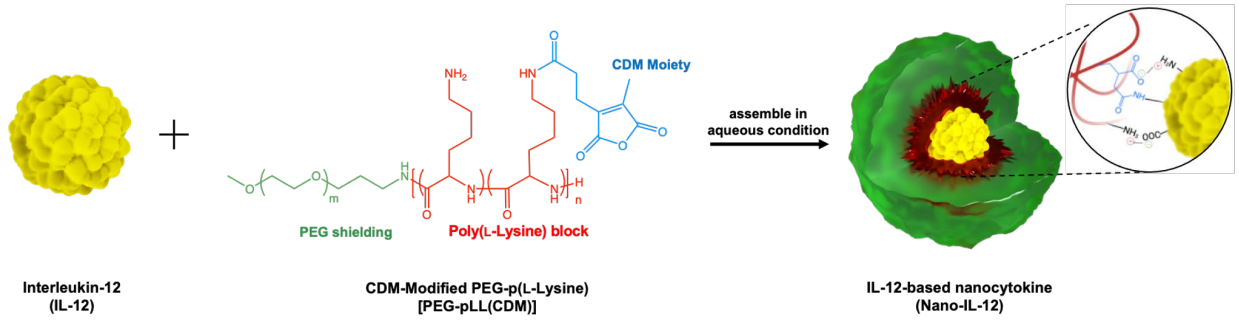

Figure 1: Nano-IL-12 is formed by simply mixing the polymer with IL-12 in aqueous condition. The particles are assembled *via* covalent bonds and electrostatic interactions between carboxyl and amine groups.

References

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