Prussian blue nanoparticle-based photothermal therapy combined with checkpoint inhibition for photothermal immunotherapy of neuroblastoma

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Neuroblastoma is the third most common pediatric cancer, and the most common extracranial solid tumor in children, accounting for 15% of cancer-related deaths in this age group. Despite improvements in diagnosis and surgical techniques, neuroblastoma remains a challenging cancer to treat due to its ability to metastasize and become resistant to conventional therapies. We therefore engineered a next-generation therapy called “photothermal immunotherapy,” which combines Prussian blue nanoparticle (PBNP)-based photothermal therapy (PTT) with anti-CTLA-4 checkpoint inhibition for treating neuroblastoma. PTT functions as a rapid and minimally invasive method for reducing tumor burden using near infrared (NIR) light-absorbing nanoparticles and a low power NIR laser. Combining PTT with the immune checkpoint inhibitor, anti-CTLA-4, reverses immunosuppression, elicits an antitumor response, and confers immunological memory. Therapeutic efficiency was tested in a syngeneic mouse model of neuroblastoma wherein the mice were intratumorally injected with PBNPs for PTT, and CTLA-4 was administered every 3 days. We found that photothermal therapy using intratumorally administered PBNPs in a mouse neuroblastoma model elicits a rapid reduction of tumor burden and growth rate, but the response is incomplete and the tumors recur. However, PBNP- combined with anti-CTLA-4 based photothermal immunotherapy results in 55% survival at 100 days. Additionally, immune response studies show that PTT elicits an infiltration of T-cells and lymphocytes to the tumor area, an immune response that is complemented by the addition of anti-CTLA-4. Depletion studies show that CD8+ and CD4+ T cells are crucial in eliciting the presented results. Finally, the photothermal immunotherapy-treated mice that survived long-term exhibited protection against neuroblastoma tumor rechallenge, suggesting the development of immunity against these tumors. Ongoing studies have built upon these findings and demonstrated the efficacy of photothermal immunotherapy in a metachronous tumor model, where treating one tumor results in complete eradication of a distal tumor. Studies where PTT is used as a “tumor vaccine” have shown a complete remission of tumor cells, elucidating the strong anti-tumor and immunological memory effect of our treatment. These results illustrate the potential of photothermal immunotherapy as a novel combination therapy for the treatment of cancer in patients with high-risk neuroblastoma due to the significantly higher tumor regression, long-term survival, and immune memory elicited by our therapy.