High Affinity of Chlorin e6 to Immunoglobulin G for Intraoperative Fluorescence Image-Guided Cancer Photodynamic and Checkpoint Blockade Therapy

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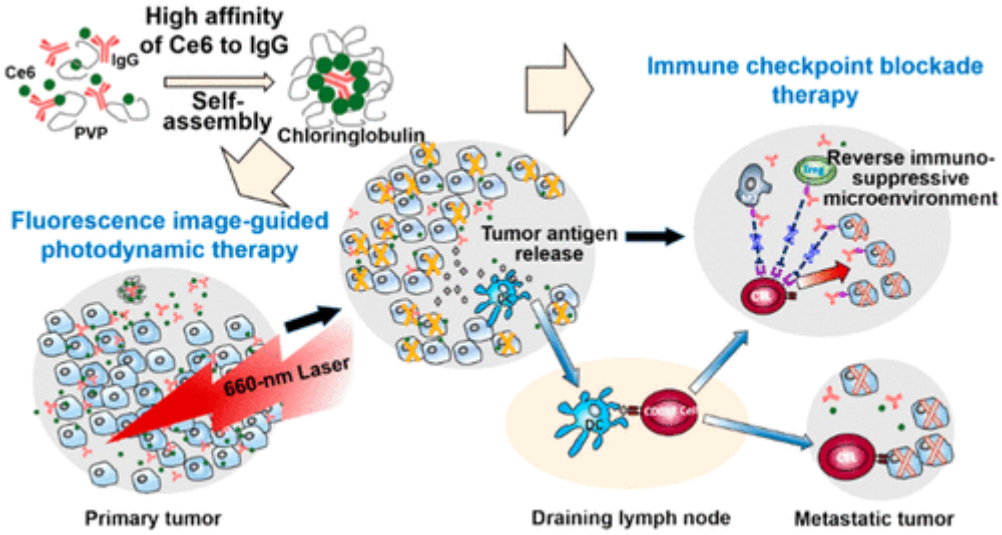
Abstract



Cancer photodynamic therapy (PDT) represents an attractive local treatment in combination with immunotherapy. Successful cancer PDT relies on image guidance to ensure the treatment accuracy. However, existing nanotechnology for co-delivery of photosensitizers and image contrast agents slows the clearance of PDT agents from the body and causes a disparity between the release profiles of the imaging and PDT agents. We have found that the photosensitizer Chlorin e6 (Ce6) is inherently bound to immunoglobulin G (IgG) in a nanomolarity range of affinity. Ce6 and IgG self-assemble to form the nanocomplexes termed Chloringlobulin (**Chlorin** e6 + immuno**globulin** G). Chloringlobulin enhances the Ce6 concentration in the tumor without changing its elimination half-life in blood. Utilizing the immune checkpoint inhibitor antiprogrammed death ligand 1 (PD-L1) (αPD-L1) to prepare αPD-L1 Chloringlobulin, we have demonstrated a combination of Ce6-based red-light fluorescence image-guided surgery, stereotactic PDT, and PD-L1 blockade therapy of mice bearing orthotopic glioma. In mice bearing an orthotopic colon cancer model, we have prepared another Chloringlobulin that allows intraoperative fluorescence image-guided PDT

in combination with PD-L1 and cytotoxic T lymphocyte antigen 4 (CTLA-4) dual checkpoint blockade therapy. The Chloringlobulin technology shows great potential for clinical translation of combinatorial intraoperative fluorescence image-guided PDT and checkpoint blockade therapy.

KEYWORDS:

- immunoglobulin G
- Chlorin e6
- fluorescence image-guided surgery
- photodynamic therapy
- programmed death ligand 1
- cytotoxic

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsnano.9b03466.

- Supporting experimental methods include cellular binding of αPD-L1, cellular uptake of the αPD-L1 Chloringlobulin *in vitro*, *in vivo* tumor distribution of Ce6 in subcutaneous CT26-Luc colon cancer model; figures include size distributions of PVP-Ce6 or Control Chloringlobulin in 10% FBS, pharmacokinetics of Ce6 in C57BL/6 mice, *in vivo* tumor distribution of Ce6 in GL261 orthotopic glioma model, *ex vivo* distribution of Ce6 in GL261 orthotopic glioma model, *ex vivo* distribution of Ce6 in mouse CT26-Luc orthotopic colorectal cancer model, cellular binding of αPD-L1 from αPD-L1 Chloringlobulin after PDT treatment, mean fluorescence intensity of Ce6 in GL261 cells following uptake of αPD-L1 Chloringlobulin *in vitro*, setup of the homemade intraoperative fluorescence imaging system, fluorescence spectrum of PVP-Ce6 or Control Chloringlobulin, *in vivo* bioluminescence imaging of CT26-Luc tumors in response to αPD-L1-αCTLA-4 Chloringlobulin treatment described in Figure 8B, bioluminescence imaging of the cured mice after subcutaneously rechallenged with the tumor cells at day 55, representative flow cytometric plots of Figure 6, representative flow cytometric plots of Figure 9, *in vivo* tumor distribution of Ce6 in subcutaneous CT26-Luc colon cancer model; tables include comparison of kinetic parameters of αPD-L1 or the prepared αPD-L1 Chloringlobulin to mouse PD-L1, the antibodies used for the flow cytometry experiments (PDF)

- **pdf**
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