# Externally Activated Nanoparticles Trigger Immunogenicity

Subjects: Oncology

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Nanoparticles activated by external energy sources, such as ionizing radiation, laser light, or magnetic fields, have attracted significant research interest as a possible modality for treating solid tumors. From producing hyperthermic conditions to generating reactive oxygen species, a wide range of externally activated mechanisms have been explored for producing cytotoxicity within tumors with high spatiotemporal control. To further improve tumoricidal effects, recent trends in the literature have focused on stimulating the immune system through externally activated treatment strategies that result in immunogenic cell death. By releasing inflammatory compounds known to initiate an immune response, treatment methods can take advantage of immune system pathways for durable and robust systemic anti-tumor response.

Keywords: Photothermal therapy ; , photodynamic therapy ; hyperthemia ; nanoparticles ; immune activation

## 1. Introduction

Nanoparticles activated by external energy sources, such as ionizing radiation, laser light, or magnetic fields, have attracted significant research interest as a possible modality for treating solid tumors. From producing hyperthermic conditions to generating reactive oxygen species, a wide range of externally activated mechanisms have been explored for producing cytotoxicity within tumors with high spatiotemporal control.

## 2. Hyperthermia

Hyperthermia is a treatment modality where either near-infrared (NIR) laser light or alternating magnetic fields can be used to locally increase the temperature of tumor tissue to 37–40 °C. Nanoparticles are used to mediate the conversion of the energy in these fields to heat, which can result in immunogenic cytotoxicity due to the stimulation of heat shock protein pathways as well as the expression of damage associated molecular patterns (cell surface calreticulin, HMGB1 expression, and extracellular ATP) and the increase in cytokine production.

## 3. Photothermal Therapy

Photothermal therapy (PTT) typically utilizes NIR lasers that penetrate deep through normal tissues (and tumors) via the so-called biological optical window where there is minimal absorption by native chromophores like oxyhemoglobin, deoxyhemoglobin, water, and melanin. Surface plasmons on the outer layer or shells of nanoparticles can be tuned to the wavelength of incident NIR light to create resonant wavelengths that efficiently convert light to heat, i.e., photothermal activation. A number of PTT nanoparticles loaded with immunotherapies have been fabricated for performing a combination of hyperthermia and immunotherapy to stimulate an antitumor immune response.

PTT can also be combined with additional processes, such as reactive oxygen species generation, to improve the cytotoxicity of NIR light, i.e., photodynamic therapy (PDT). Both PTT and PDT generate reactive oxygen species and stimulate immunogenic cell death, pro-inflammatory cytokine elaboration, dendritic cell maturation in tumor-draining lymph nodes and CD8 T cell activation. When coupled with immune checkpoint blockade or other such immunotherapy, this effect can be amplified even further. They can also be coupled with traditional anti-cancer therapies like chemotherapy and radiation therapy.

## 4. Alternating Magnetic Fields

Magnetic field hyperthermia is a cancer treatment strategy that utilizes magnetic nanoparticles, typically ferrites, activated by alternating magnetic fields. Under these alternating fields, magnetic nanoparticles exhibit hysteresis, which produces localized heat, and thereby results in tumor cytotoxicity.

## 5. Photodynamic Therapy

Photodynamic therapy (PDT) is the process whereby a photosensitizer, generally activated by a UV-vis light source, produces reactive oxygen species (ROS) in the tumor, resulting in cytotoxicity. Due to the ability of ROS to result in necrotic cell death, there has been significant interest in studying the immunogenic effects of PDT.

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