



The ability of one structural type to perform multiple medical diagnostic or therapeutic functions is often cited as an advantageous characteristic of nanomaterials that cannot be achieved with organic small molecules.^[1–3] Although there are now many examples of nanosystems that integrate multiple functions into a single structure, the designs can reduce the efficacy of the individual functions due to space and surface-chemistry limitations in the tiny platforms. For example, magnetic nanoparticles and drug molecules can be co-encapsulated in liposomes to simultaneously perform multiple functions, such as magnetic resonance imaging, magnetic drug delivery and hyperthermia,^[4] but the loading capacity and the stability are typically compromised relative to a single-component liposome. There has been some effort to develop intrinsically multifunctional nanomaterials such as magnetic nanocapsules and luminescent porous silicon nanoparticles to overcome such problems,^[5,6] although these more complicated structures may lose versatility in terms of the types of payloads they can carry. Access to the payloads can also be limited, reducing the ability to control their release. Separating functions into two or more nanoparticle formulations is one means to simplify the problem. If two separate nanomaterials can be engineered to synergistically cooperate in their diagnostic or therapeutic functions, it is possible that the overall dosage can be reduced, minimizing side effects and providing a safer transition to the clinic.

Combination therapies are commonly employed in a wide range of cancer treatments. In particular, hyperthermia can increase the concentration of an administered therapeutic

nanoparticle in a tumoral region by increasing blood flow and vessel permeability.^[7,8] Hyperthermia can also enhance drug toxicity in cancer cells that are otherwise resistant to chemotherapeutics.^[9] Furthermore, local hyperthermia can improve the accumulation of a drug, which is encapsulated in a thermosensitive carrier.^[10,11] The combination of hyperthermia and chemotherapeutics can, therefore, be employed synergistically to treat high-risk tumors with a goal of total tumor eradication. From a clinical perspective, precise and site-specific heat transfer to a diseased site would improve the safety and efficacy of thermal cancer therapies.

Recent advances in the field of plasmonic nanomaterials have presented new opportunities for localized hyperthermia therapy. Plasmonic nanomaterials are metallic structures that efficiently convert optical radiation into heat by coupling into one or more plasmon modes.^[12,13] Of particular interest are gold nanorods (GNRs) due to their large optical coefficients in the NIR region of the spectrum, where living tissue is highly transparent.^[14,15] Previously, we and other groups demonstrated that GNRs can be modified to circulate for long periods of time in the blood stream and passively accumulate in tumors *in vivo*, where they can be heated with localized NIR radiation to selectively destroy malignant tissue regions.^[16–18] In addition, the optical properties of GNRs or gold-based nanoparticles have been harnessed to image targeted tissues *in vivo*.^[19–21] In this Communication, we hypothesized that GNRs could be used to detect a diseased site and act as tumor-specific triggers to amplify the therapeutic function of a circulating drug carrier (Fig. 1a). We find that GNR-mediated photothermal heating is highly localized in tumors and significantly improves the selectivity and efficacy of cancer treatment with thermosensitive drug carriers.

Cetyltrimethylammonium bromide (CTAB)-coated GNRs were coated with a mixed monolayer of poly(ethylene glycol) (PEG) and surface-enhanced Raman scattering (SERS)-active reporter molecules to increase circulation times, reduce *in vivo* toxicity, and provide remote imaging as described previously.^[18,22] The gold cores appear as dark rods in the transmission electron microscopy (TEM) image (Fig. 1b), with an average width of ~13 nm and length of ~47 nm. The PEG coating is observed as a faint halo around the metal cores. The wavelength of maximum optical absorption of the GNR is 800 nm (Supporting Information, Fig. S1). As observed previously, intravenously injected PEG-coated GNRs were observed to circulate in the blood stream with a half-life of >17 h in mice, enabling passive accumulation in a xenografted MDA-MB-435 human melanoma tumor through the porous vascular structures.^[18] Passive accumulation in tumors allowed tunable photothermal heating selectively in the tumor region by excitation with an 810 nm laser

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