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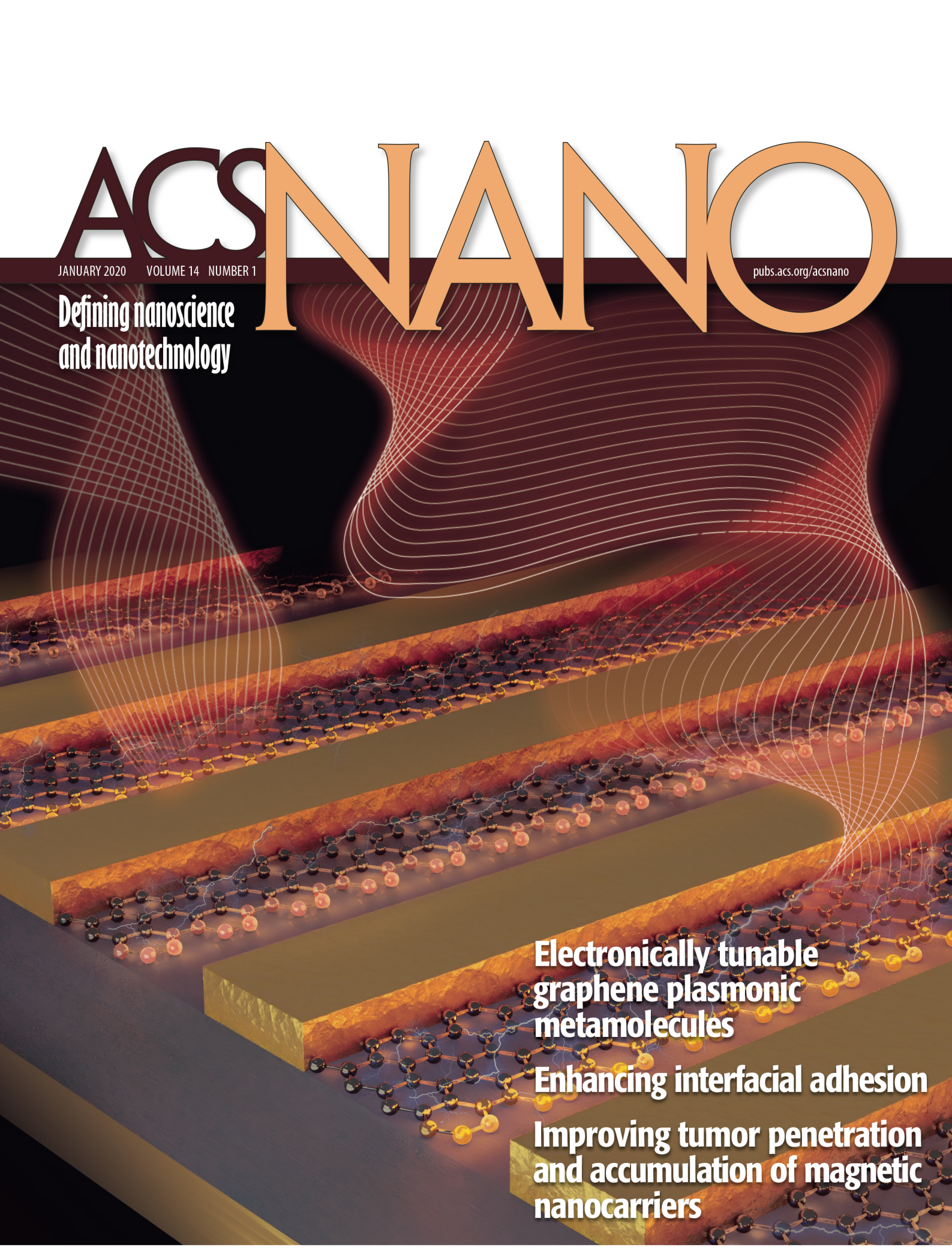

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ARTICLE

Combined Magnetic Hyperthermia and Immune Therapy for Primary and Metastatic Tumor Treatments

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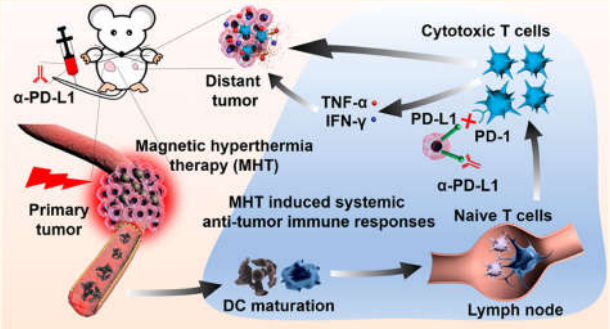
ABSTRACT: Cancer immunotherapy shows promising potential in future cancer treatment but unfortunately is clinically unsatisfactory due to the low therapeutic efficacy and the possible severe immunotoxicity. Here we show a combined magnetic hyperthermia therapy (MHT) and checkpoint blockade immunotherapy for both primary tumor ablation and mimetic metastatic tumor inhibition. Monodispersed, high-performance superparamagnetic $CoFe_2O_4$@$MnFe_2O_4$ nanoparticles were synthesized and used for effective MHT-induced thermal ablation of primary tumors. Simultaneously, numerous tumor-associated antigens were produced to promote the maturation and activation of dendritic cells (DCs) and cytotoxic T cells for effective immunotherapy of distant mimetic metastatic tumors in a tumor-bearing mice model. The combined MHT and checkpoint blockade immunotherapy demonstrate the great potentials in the fight against both primary and metastatic tumors.



KEYWORDS: *cancer, core−shell structure, magnetic hyperthermia therapy, checkpoint blockade immunotherapy, bilateral tumor model*

Despite the great efforts devoted, cancer remains one of the most lethal diseases because of cancer metastases, which is the major contributor to the high mortality of cancer patients.[1] Cancer immunotherapy can induce immune responses in patients and has potentials as a future therapeutic modality for metastatic tumors. Therefore, great attention has been paid to cancer immunotherapy in recent years along with the ever-deeper understanding of the interactions between cancer and the immune system.[2,3] Among cancer immunotherapies, immune checkpoint blockade therapy blocks negative immune regulatory pathways by antibodies and has achieved a certain level of clinical success for cancer treatment.[4,5] Even so, immune checkpoint therapy has only benefited a small fraction of patients due to the insufficient activation of the immune system.[4,5] Therefore, great efforts have been made to combine diverse treatments for primary and metastatic tumors with immune checkpoint therapy to enhance the immune responses, such as cryoablation,[6−8] radiotherapy,[9−11] chemotherapy,[12] photothermal therapy,[13−15] and photodynamic therapy.[16−18] Nevertheless, radiotherapy and chemotherapy cause severe side effects in patients in the clinic. The extensively explored photothermal therapy (PTT) uses near-infrared (NIR) light to treat tumors, while photodynamic therapy (PDT) employs UV/vis light to treat tumors, which can be hard to use to deal with deep-seated tumors due to limitations of light penetration. Hence, it is critical to find an effective way to efficiently and safely induce and promote immune responses against tumors.

In recent years, ever-increasing attention has been paid to magnetic hyperthermia therapy (MHT) because of its great effectiveness, noninvasive property, minimized damage to normal tissues, low cost, and excellent tissue penetration.[19] In a typical MHT process, magnetic nanoparticles can generate a considerable amount of heat in tumor regions to kill tumor cells by applying an alternating magnetic field (AMF).[20] In the meantime, tumor-associated antigens could be generated, which may possibly induce and promote immune responses. However, few reports can be found on the combination of MHT with immune checkpoint blockade therapy for cancer

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