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Review article

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# Thermal immuno-nanomedicine in cancer

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## Abstract

Immunotherapy has revolutionized the treatment of patients with cancer. However, promoting antitumour immunity in patients with tumours that are resistant to these therapies remains a challenge. Thermal therapies provide a promising immune-adjuvant strategy for use with immunotherapy, mostly owing to the capacity to reprogramme the tumour microenvironment through induction of immunogenic cell death, which also promotes the recruitment of endogenous immune cells. Thus, thermal immunotherapeutic strategies for various cancers are an area of considerable research interest. In this Review, we describe the role of the various thermal therapies and provide an update on attempts to combine these with immunotherapies in clinical trials. We also provide an overview of the preclinical development of various thermal immuno-nanomedicines, which are capable of combining thermal therapies with various immunotherapy strategies in a single therapeutic platform. Finally, we discuss the challenges associated with the clinical translation of thermal immuno-nanomedicines and emphasize the importance of multidisciplinary and inter-professional collaboration to facilitate the optimal translation of this technology from bench to bedside.

## Sections



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## Key points

- Immunotherapy has revolutionized cancer therapy, and the clinical effectiveness of approaches such as immune-checkpoint inhibitors and cellular immunotherapies has created substantial improvements in outcomes.
- Thermal therapies designed to deliver local hyperthermia can promote antitumour immunity via the induction of immunogenic cell death following tumour ablation and by reprogramming the tumour microenvironment.
- Several early-phase trials combining thermal therapies with immunotherapy are either ongoing or completed, and some have provided encouraging results that support the further clinical development of combined thermal therapy–immunotherapy approaches.
- Thermal immuno-nanomedicines are thermal therapies that also incorporate immunotherapies within a single nanoparticle, potentially enabling simultaneous activity and synergy between these two modalities.
- Preclinical evidence suggests that thermal immuno-nanomedicines provide a promising cancer therapeutic strategy; however, coordinated efforts from multidisciplinary teams of experts will be required to drive the clinical translation of this technology.

## Introduction

Immunotherapy has revolutionized cancer therapy. Several clinically effective cancer immunotherapy strategies have been established, including immune-checkpoint inhibition, vaccination and adoptive T cell transfer, comprising chimeric antigen receptor (CAR)-engineered and T cell receptor (TCR)-engineered T cell therapies[1–6]. However, cancers have a notorious ability to evade the immune system, and tumours that are not inflamed and/or that do not elicit an immune response, so-called 'cold' tumours, often do not respond to immunotherapies[7–10]. Furthermore, the immunosuppressive tumour microenvironment (TME) often acts as a barrier to immune cell infiltration that enables the tumour to evade immune surveillance, leading to tumour progression[11–13]. Accordingly, methods of reprogramming the TME to convert cold tumours to hot tumours and thus improve the efficacy of immunotherapy are a focus of considerable research interest.

To address these challenges, strategies combining immunotherapy with other therapeutic modalities have been developed and tested both in preclinical models and in clinical trials[14–20]. For example, more than eight regimens combining immune-checkpoint inhibitors (ICIs) with chemotherapy have been approved by the FDA for patients with metastatic non-small-cell lung cancer (NSCLC) and the combination of ICIs with radiotherapy is being explored for the same indication in several trials (including NCT03867175, NCT03774732, NCT03446911)[21–23]. Thermal therapy, which involves heating either the whole body or local areas, such as the tumour site, is a field of increasing research interest, mostly owing to the capacity to improve clinical responses to radiotherapy, chemotherapy and immunotherapy in patients with, among others, breast cancer, colon cancer or central nervous system cancers[24–29]. Thus, the FDA has approved several devices designed to deliver thermal therapies, including high-intensity focused ultrasound (HIFU) and radiofrequency ablation (RFA), for hepatocellular carcinomas (HCCs), liver metastases and renal cell carcinomas as well as other cancers[30,31] (Tables 1 and 2).

Thermal therapy has been shown to induce immunogenic cell death (ICD) of cancer cells, which promotes both innate and adaptive immunity in preclinical models[32–34] (Fig. 1). Moreover, thermal therapy improves perfusion and reduces intratumour interstitial pressure, most likely owing to a transient increase in vascular permeability[26], which promotes the accumulation of therapeutic co-stimulatory molecules and/or immune cells and facilitates the release of pro-inflammatory cytokines and chemokines that can overcome an immunosuppressive TME[35–38]. Various clinical trials combining thermal therapy and immunotherapy have been conducted and could lead to advances in cancer therapy[39–41].

Despite the encouraging performance of thermal immunotherapy in preclinical models[41,42], several limitations exist that are likely to impair the therapeutic effectiveness of this approach in patients with cancer. Firstly, the usually systemic administration and non-specific accumulation of immunotherapeutic and/or thermotherapeutic agents not only influence their antitumour activities but also can result in adverse events[43]; secondly, in the future, gene-editing technologies are increasingly likely to be employed to modify tumour cells and/or their microenvironment, including regulating the expression of immune checkpoints and, potentially, of other targets of interest, and this will require safe and effective transfection systems[44–46]. Data from an increasing number of studies demonstrate that nanomedicines have considerable potential to overcome these challenges owing to several unique advantages over traditional drug formulations, such as enhanced targeting capacity, intracellular delivery, controlled release of therapeutic agents, bioavailability and multi-functionality. Thus, thermal immuno-nanomedicines (TINs), which involve the nanoparticle-mediated delivery of thermal therapies alongside an immunotherapeutic agent that enables simultaneous synergy with thermal therapy, are an area of rapidly developing research interest[34,47,48].

In this Review, we summarize the current status and development of thermal therapies and attempt to combine these therapies with immunotherapies. We provide an overview of the various TIN strategies, which have the potential to deliver various thermal therapies combined with other cutting-edge immunotherapy approaches. We also highlight the challenges that are likely to arise in the clinical translation of TINs and emphasize the importance of coordinated multidisciplinary teams comprising experts with various professional backgrounds to optimize clinical translation.

## Thermal therapies

The activity of biological systems is profoundly affected by even small elevations in temperature. A well-controlled increase in temperature can support the treatment of various diseases, including cancer[49–51]. Over the past few decades, substantial progress has been made in developing different heating techniques with improved temperature control that maximize therapeutic efficacy while minimizing the risk of adverse events. According to the extent of the temperature increment, therapeutic heating modalities can be broadly categorized as hyperthermia or thermal ablation.

Hyperthermia refers to mild, transient elevations in tissue temperature to a maximum of 45 °C (ref. 52). Clinically, regional hyperthermia can improve the therapeutic effect of more traditional therapies through various mechanisms such as the promotion of blood flow

**Table 1 | Commonly used electromagnetic thermal therapeutic devices for cancer therapy**

| Device | Cancer type | Main features |
|---|---|---|
| **RFA** | | |
| Cool-tip RFA system (Valleylab/Radionics/Covidien, USA)[256] | Unresectable liver lesions (primary or metastatic)[71] | Monopolar equipment; straight-needle design; maximum energy delivery (E series) |
| RITA StarBurst RFA system (AngioDynamics, USA)[257] | Primary liver tumours[72], metastases from primary CRCs[75] | Multipolar equipment; real-time tissue monitoring at the margins of the ablation |
| RF 3000 RFA system with LeVeen needle electrodes (Boston Scientific, USA)[258] | Primary HCCs[73] | Multipolar equipment; wide portfolio matrix of array diameters from 2 to 5 cm; soloist single-needle electrode for small 1.5 cm×1 cm ablation zones |
| Celon Olympus (Medical and Industrial Equipment, UK)[259] | HCCs[74], RCCs[76], osteoid osteomas[81] | Integration of bipolar and multipolar probes into a single equipment; intratumoural and extratumoural (no-touch technique) placement of applicators; large range of ablation diameters (5–90 mm); optimized treatment by resistance-controlled automatic power |
| HALO$^{360+}$ bipolar RFA system (Covidien GI Solutions, USA)[260] | Barrett oesophagus[77] | Automated radiofrequency energy delivery; fixed amount of radiofrequency energy density; fixed power; bipolar electrode array |
| HALO$^{90}$ RFA system (Covidien GI Solutions, USA)[261] | Barrett oesophagus[78] | Used for secondary RFA of residual oesophageal lesions after initial circumferential ablation using the HALO$^{360+}$ system |
| OsteoCool RFA system (Medtronic, USA)[262] | Spinal metastases[80] | Coaxial and bipolar technology delivers RFA, cooled with circulating water |
| OptaBlate Bone Tumour Ablation System (Stryker, USA)[263] | Bone tumours | Microinfusion technology enabling the concurrent treatment of two vertebral body levels using a bipedicular approach |
| S-5L RFA system (MedSphere International, China)[79] | Mixed thyroid nodules[79] | Simultaneously compatible with internally cooled and normal system; dual-mode control-power control and temperature control; real-time temperature, power and resistance feedback |
| **MWA** | | |
| Emprint ablation system (Medtronic, USA)[264] | Primary HCCs or liver metastases[87] | Thermosphere technology to control the microwave field and length of the microwaves; more spherical and more predictable ablations |
| NeuWave Certus MWA system (NeuWave Medical, USA)[265] | Primary HCCs or liver metastases[88] | Probe–multiprobe synchrony helps to protect non-target tissues; versatile probe portfolio to control the ablation size, shape and position; reduced blood loss, procedure time and length of hospital stay with pre-transection coagulation |
| HS AMICA (HS Hospital Service, Italy)[266] | HCCs[90], bone metastases[93] | Capable of both microwave and radiofrequency energy generation, delivery and monitoring; embedded peristaltic pump enables internal cooling of either type of applicator |
| Acculis MWA system (AngioDynamics, USA)[267] | NSCLCs[92], HCCs[91] | The fastest device in achieving the largest coagulation diameter (short-axis) at 5 and 6 min; predictable ablation zones |
| Evident MWA System (Covidien, USA)[268] | HCCs, CRCs[61] | Minimized set-up, simultaneous antenna use, multiple-use antennas |
| **LITT** | | |
| Visualase Thermal Therapy System (Medtronic, USA)[269] | Meningiomas, ependymoma, gliomas[62] | 980-nm laser with power of 15 W; capable of MRI-guided laser ablation; smallest laser catheter (1.65 mm in diameter) on the market; requires minimal sutures, typically a single stitch; requires no ionizing radiation or large skull flap |
| NeuroBlate System (Monteris Medical, Canada)[270] | Meningiomas[63], gliomas[64] | 1,064-nm laser with power of 12 W; MRI-guided laser ablation; robotically controlled probe driver; mini-bolt access; side-firing probes for treatment of irregularly shaped lesions |

CRC, colorectal cancer; HCC, hepatocellular carcinoma; LITT, laser interstitial thermal therapy; MWA, microwave ablation; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; RFA, radiofrequency ablation.

resulting in tumour reoxygenation (39–44 °C), prevention of DNA damage repair (>41 °C) and activation of an antitumour immune response[53,54]. Thermal ablation refers to the application of high temperatures (>50 °C) to directly damage tumour cells via coagulation and protein denaturation. Clinically, thermal ablation has been recognized as a minimally invasive alternative to certain surgical procedures such as ablation of early-stage HCCs[55]. Owing to differences in energy transduction and delivery techniques between high-grade heating devices, the heating depth, direction and volume can all vary between devices, each with its own advantages and disadvantages[50]. In this section, common thermal therapeutic modalities and their applications in the clinic are described in detail (Tables 1 and 2 and Fig. 2).

## Electromagnetic thermal therapy

Electromagnetic thermal therapy harnesses the thermal energy produced by a high-frequency alternating sinusoidal electromagnetic field. Two main mechanisms of heat generation are involved in electromagnetic heating: dielectric heating and ionic conduction. Polar molecules, such as water, preferentially align in succession in the alternating electromagnetic field owing to their inherent electric dipole moment upon exposure to an alternating current. As a consequence, these molecules acutely rotate with frequencies in the MHz range and the obtained excessive kinetic energy then dissipates owing to collisions with other molecules, leading to so-called dielectric heating[56]. Ions located in tissues generally oscillate in response to

electromagnetic stimulation in the kilohertz range[57]. Owing to an abundance of neighbouring molecules and atoms, the oscillation of ions and the resultant dispersal of kinetic energy form an effective method of generating heat[57].

Three main electromagnetic heating-based thermal therapy modalities — RFA, microwave ablation (MWA) and photothermal therapy (PTT) — are currently being either applied in clinical practice or investigated in clinical trials[51,58–64]. The clinical applications of PTT, including laser interstitial thermal therapy, have been comprehensively reviewed elsewhere[65]; therefore, this discussion is focused on RFA and MWA. Several commercially available interstitial heating devices are currently available. For most devices used during both RFA and MWA, a needle-shaped catheter is surgically implanted into the targeted tissues, often with guidance by medical imaging, and heat is then generated locally via the catheter, known as interstitial heating.

**Radiofrequency ablation.** RFA is currently the most widely used clinical electromagnetic ablative modality and has the advantages of minimal invasiveness and a limited risk of adverse events, making this approach a reasonable option when surgical resection is inadvisable[66–69]. To deliver RFA, a slender probe is inserted into the tumour tissues with imaging guidance, followed by the creation of an alternating current (350–500 kHz) within the target tissues. The probes, also known as RFA electrodes, can be divided into single-tip monopolar probes and multipolar cluster arrays with the former requiring grounding pads to close the electric circuit. To achieve the desired anchoring and ablation profiles, umbrella-shaped clustered electrodes have also been developed. In this scenario, a carefully controlled amount of energy is delivered to the tumour through the electrodes to induce a uniform heating zone in direct proximity to the probe[70]. The electrical conductivity of the target tissue is usually enhanced, for example, using intratumoural saline injections, to deliver a sufficiently high temperature to cover the entire target tissue. Some other functional probes, such as multitoned expandable probes, needle perfusion probes and cool-tip probes, are also available for different application scenarios[57]. Several RFA devices have been approved by the FDA for clinical application in the USA, including the Cool-Tip RFA system, the OsteoCool RF ablation system and the OptaBlate ablation system (Table 1). Clinical indications for RFA include several thoracic and gastrointestinal tumours, including liver lesions[71–74], colorectal cancers[75], renal cell carcinomas[76], oesophageal cancers[77,78], thyroid nodules[79], spinal metastases[80] and osteoid osteomas[81]. An example of the effectiveness of RFA is provided by a multicentre, open-label trial in which 90 patients with liver cancer with a Child–Pugh classification of A or B and either multiple (≤3 in number and ≤3 cm in diameter) or solitary (≤4 cm in diameter) lesions underwent bipolar RFA using the Celon Olympus RFA system. Complete tumour necrosis was achieved in 97.8% of patients. Three patients had adverse events requiring hospitalization (abdominal wall burn, pleural effusion and biliary peritonitis)[82].

**Microwave ablation.** MWA provides another method of inducing immediate coagulation necrosis of the target lesion as seen with RFA. During MWA, microwaves with specific frequencies (typically 915–2,450 MHz) are generated using a magnetron in a microwave therapeutic apparatus and delivered to tumour tissues through an intratumourally placed needle-shaped antenna. Similar to RFA, dielectric heating from the inherent dipoles is responsible for thermogenesis for MWA[83]. However, unlike RFA, MWA does not require an electric current, which alleviates the concerns regarding tissue desiccation during the therapeutic process, which can compromise the therapeutic effectiveness of RFA. This important difference in heat source makes MWA more appropriate for lesions located in tissues with higher impedance and limited thermal conduction such as lung and bone[84]. High-frequency MWA (≥2,450 MHz) typically generates an ablation area that is smaller and rounder than that obtained with low-frequency MWA, making this method more suitable for the ablation of small, round tumours, while avoiding damage to surrounding non-malignant tissues. Thus, predicting the size of the ablation zone becomes easier with high-frequency MWA. However, lower-frequency MWA has the advantage of deeper tissue penetration and higher energy conversion

**Table 2 | Commonly used HIFU systems for cancer therapy**

| Device | Cancer type | Main features |
|---|---|---|
| Sonablate system (innoMedicus, Austria)[271] | Prostate cancer[99] | Transrectal HIFU system; targets specific tissues using ultrasound MR fusion; enables ablation with pinpoint accuracy while sparing untargeted tissues; analysis using real-time imaging and advanced tissue change monitoring technology |
| Ablatherm system (EDAP TMS, USA)[272] | Prostate cancer[100] | Transrectal HIFU system; MR images and biopsy maps imported for automatic matching of ultrasound images; robotic procedure; preservation of surrounding tissue with different treatment strategies (whole gland/nerve sparing/partial gland) |
| TULSA-PRO system (Profound, USA)[273] | Prostate cancer[101] | Transurethral HIFU system; MRI-guided device positioning; robotically driven ultrasound ablation with closed-loop thermal feedback control; capable of sweeping ultrasound and continuous rotation; capable of treating both large and small prostate volumes, anterior and posterior prostate tissues; enables thermal protection of urethra and rectum |
| ExAblate system (Insightec, Israel)[274] | Prostate cancer[96] | Enables real-time therapeutic monitoring |
| Sonalleve system (Profound, USA)[275] | Desmoid tumours[106], breast cancer[105], osteoid osteomas[103] | Enables real-time MRI temperature monitoring and control; reduced cooling time between sonications with direct skin cooling and dual-mode thermometry |
| Haifu Model JC (Chongqing Haifu Medical Technology, China)[276] | Primary HCCs or metastases, pancreatic cancers[107], RCCs[109] | Enables conformal and precise ablation; one-off treatment, not limited by tumour size and shape; real-time ultrasound-guided therapy with digital quantitative analysis |
| HIFUNIT9000 (Shanghai A&S Science Technology Development, China)[277] | Pancreatic cancers[108] | Real-time ultrasound-guided therapy; enables intelligent three-dimensional reconstruction of tumours; multiple arrays and double focuses |

HCC, hepatocellular carcinoma; HIFU, high-intensity focused ultrasound; RCC, renal cell carcinoma.

efficiency, which are both beneficial when treating larger tumours[85,86]. Thus far, two MWA devices, Emprint and Evident MWA, have received FDA approval for the treatment of patients with liver tumours, including primary HCCs and liver metastases (Table 1). To evaluate the efficacy of Emprint MWA for the ablation of unresectable large-diameter liver lesions (≥3 cm in diameter), 21 patients with such tumours (mean diameter of 34.7 mm) underwent percutaneous MWA. The shape and volume of the ablation zones were evaluated using CT imaging within the month before and the month after treatment. Residual tumour material was observed in only 4.8% of tumours after a single ablation session, suggesting that this approach provides an effective treatment option for patients with unresectable large-volume liver lesions[87]. In addition to liver tumours[61,88–91], MWA is also widely used for the ablation of tumours of the lungs[92], bones[93] and pancreas[94].

### High-intensity focused ultrasound

HIFU is the only truly non-invasive thermal therapy. Furthermore, no upper limit of tissue tolerance exists, enabling patients to receive repeat HIFU procedures as often as is necessary[95,96]. During HIFU, ultrasound waves (typically 0.8–3.5 MHz) are focused on a specific focal zone using a curved transducer, phased array or lens, leading to the highest wave pressure at a small target lesion with negligible off-target exposure. HIFU devices typically have a target area that is ellipsoidal in shape (1–3 mm in diameter and 8–15 mm in length); therefore, many of these target areas must be placed side by side to cover the entire tumour. HIFU has the advantage of avoiding the possibility of tumour seeding along the needle track during treatment, which can lead to the development of haematogenous metastases in patients receiving electromagnetic thermal ablation[97].

Two predominant principles, including temperature increment and cavitation, are highly relevant to the biological effects of HIFU ablation[98]. Under the stresses created by ultrasound pressure, the vibration or rotation of molecules in the tissue could be intensified, which makes the collision of these molecules with others more frequent, resulting in some loss of energy owing to friction, also known as frictional loss. Moreover, heat can be produced by frictional loss following intramolecular collisions, which can cause an immediate (within seconds) increase in temperature and irreversible coagulative necrosis of target tissues. Cavitation refers to the vibration of bubbles in response to ultrasound pressure waves. These bubbles are generated

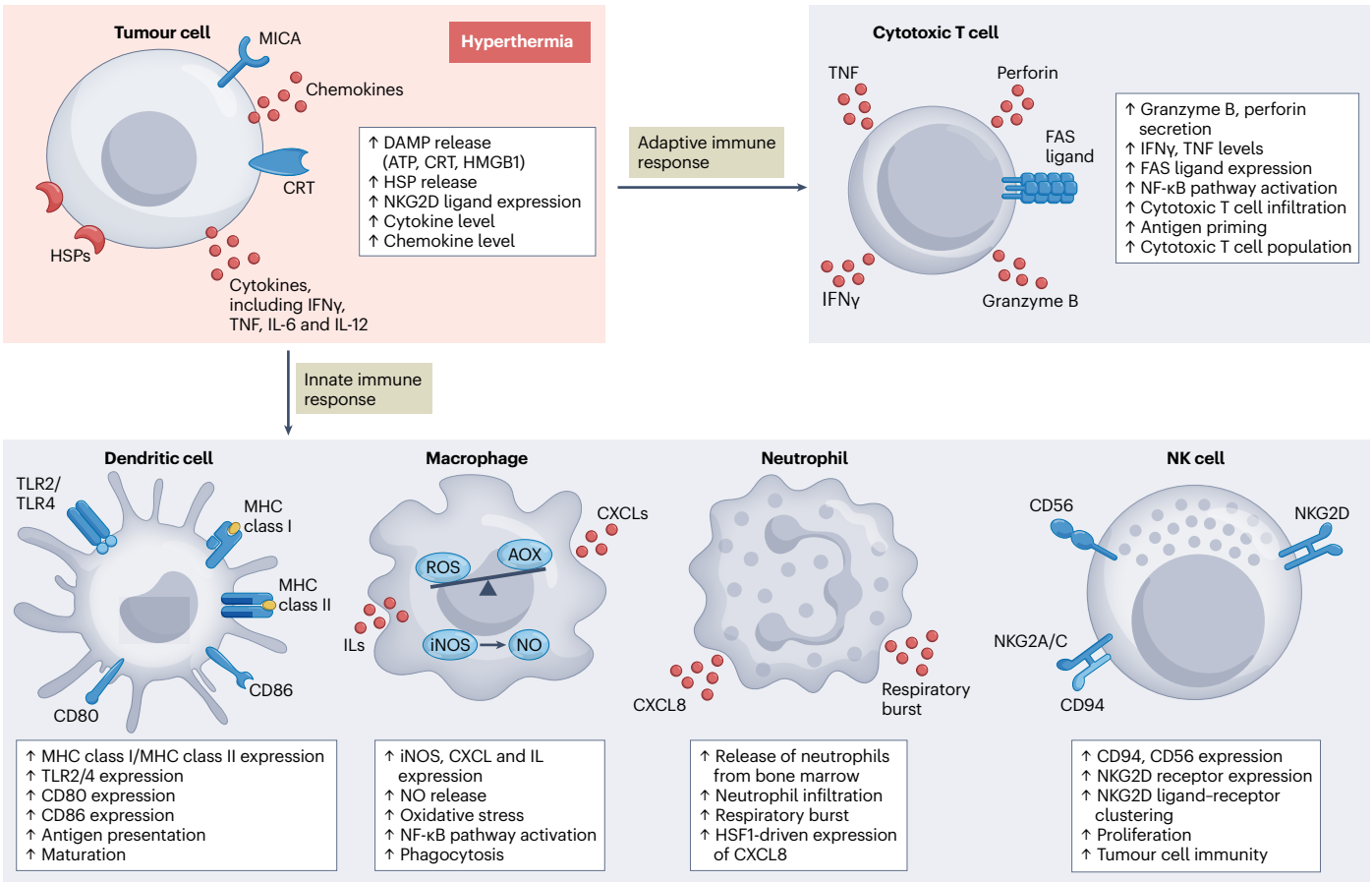



**Fig. 1 | Effects of hyperthermia on innate and adaptive immunity.** Hyperthermia (typically 41–43 °C in most clinical applications) can induce immunogenic cell death of tumour cells, which results in the release of damage-associated molecular patterns (DAMPs, including ATP, calreticulin (CRT) and high mobility group box 1 (HMGB1)) and heat-shock proteins (HSPs), increases the expression of several biomarkers of immune cell activation, such as NKG2D and MICA, and promotes the release of several pro-inflammatory cytokines and chemokines, which are able to further enhance the activation of different immune cells to boost both innate and adaptive immunity and promote tumour microenvironment remodelling. AOX, alternative oxidase; ILs, interleukins; iNOS, inducible nitric oxide synthase; NK, natural killer; NO, nitric oxide; ROS, reactive oxygen species; TLR, Toll-like receptor.

in a liquid when the tensile strength of the liquid is exceeded owing to the external ultrasound pressure waves. Where such waves reach sufficient frequency and amplitude, the liquid separates or fractures to form voids, which are then filled with air and/or the liquid itself. These voids, also known as gas nuclei, are rarified cavities that are able to further grow and collapse in response to more ultrasound waves, undergoing so-called stable cavitation and inertial cavitation. The stable cavitation caused by the oscillation of bubbles usually places mechanical stress on both vessel walls and cell membranes, resulting in improved extravasation of drugs into target tissues as well as their intracellular delivery. Inertial cavitation, generated by the collapse of bubbles upon ultrasound stimulation beyond a certain energy threshold, can introduce dramatic localized increases in temperature and shockwaves, leading to necrosis owing to mechanical stress and thermal invasion.

So far, the FDA has approved several HIFU devices, including the Sonablate and Ablatherm systems (transrectal HIFU) and the TULSA-PRO system (transurethral HIFU) for the ablation of primary prostate tumours[99–101], and the Sonalleve and ExAblate systems for osteoid osteomas and uterine fibroids, respectively[30,102–104] (Table 2). HIFU can also be used for other indications, including breast cancers[105], desmoid tumours[106], liver cancers[107], pancreatic cancers[108] and kidney cancers[109]. Device positioning for target tumours is usually guided by MRI, which can also provide the necessary real-time temperature feedback for robotically driven HIFU ablation[110,111]. In an early clinical study, 70 patients with T1c–T2a cancers of any Gleason score limited to one side of the prostate received focal HIFU using the Sonablate system; 7 patients also received neoadjuvant androgen-deprivation therapy. Residual tumour material was detected in 11.9% and 18.4% of patients at 6 months and 12 months post-treatment, respectively. Adverse effects included urethral strictures and urinary tract infections in 8.6–4% and 11.4–4% of patients, respectively, depending on the area of the prostate that was ablated[112]. Immediate tissue responses during HIFU can be observed using advanced technologies to evaluate therapeutic effectiveness. For example, tissue change monitoring is a quantitative software module that can be applied alongside the Sonablate system to evaluate the adequacy of energy delivery to each HIFU ablation site. In this system, a radiofrequency signal is sent to a targeted ablation site before and after HIFU with quantification based on comparisons of radiofrequency pulse-echo ultrasound signals at each HIFU lesion. Finally, an easy-to-read on-screen colour overlay with focal point markers is displayed to guide HIFU delivery. For the Sonalleve MR-HIFU system, which was approved for patients with osteoid osteoma of the extremities by the FDA in 2020, a self-contained cooling system is included in which cooled water is circulated within the ultrasound window during treatment, thus protecting tissues immediately surrounding the ablation zone.

### Magnetic hyperthermia

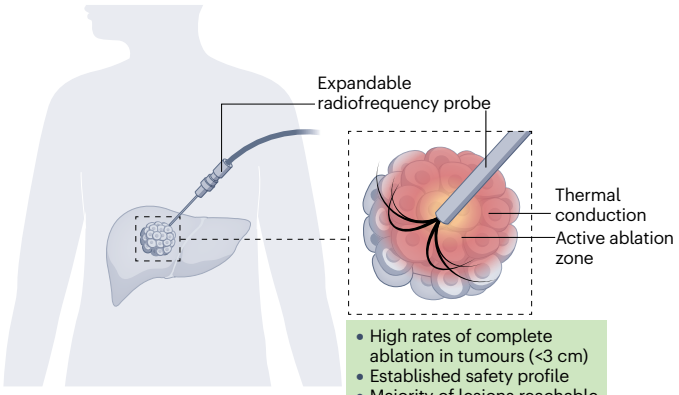
Magnetic hyperthermia is another important thermal therapeutic modality that is currently in clinical use. In this method, a series of magnetic particles are prepared as transducers enabling the highly efficient conversion of electromagnetic energy into heat when subjected to an alternating magnetic field[113]. Nanoparticle-mediated hyperthermia is induced by the coupling of magnetic moments of the atoms in the nanoparticles within the imposed time-dependent external magnetic field (with a typical radiofrequency range of 100–300 kHz)[114–117]. Nanoparticle-mediated magnetic hyperthermia can enhance the local temperature of the tumour within the range of 42–46 °C, resulting in cell death via either apoptosis or necrosis[116,118]. Magnetic nanoparticles are administered intratumourally with the purpose of maximizing the intratumoural concentration of the nanoparticles, which is a crucial determinant of heat generation. In 2012, a magnetic hyperthermia device was approved by the EMA as an adjunct therapy for patients with recurrent glioblastoma who are also receiving radiotherapy[119]. In 2021, a clinical trial testing a similar approach for tumour ablation in men with prostate cancer received ethics approval (NCT05010759).

## Combinations with immunotherapy

In addition to causing direct damage to tumour tissues, thermal therapies might also induce a systemic anticancer immune response, providing an opportunity to eradicate both primary tumours and their metastases (Fig. 1). The targeted thermal stress generated by such therapies can cause ICD, leading to the release of damage-associated molecular patterns such as calreticulin, heat-shock proteins (HSPs), ATP and high mobility group box 1 (HMGB1)[18,120]. These damage-associated molecular patterns act as 'find me' signals (ATP and HMGB1) or 'eat me' signals (HSPs and calreticulin) that, with the help of chemokines, mobilize antigen-presenting cells and their precursors to tumours, resulting in the reversal of immunosuppression and establishing a favourable immunogenic TME[121–124]. Thermal stimulation has also been shown to promote the differentiation of regulatory T ($T_{reg}$) cells into T helper 17 ($T_H17$) cells via hyperthermia-induced IL-6 secretion, which promotes antitumour activity in preclinical models[125]. Similarly, $CD8^+$ T cell function can be promoted by mild thermal stimulation as demonstrated by increased antigen-dependent activity and activation-induced IFNγ release at 39.5 °C relative to 33 °C and 37 °C, respectively, in preclinical models[126]. Meanwhile, activation of other innate immune cells, including natural killer (NK) cells, macrophages and neutrophils, as well as dendritic cell (DC) maturation are promoted upon heating[127–129]. For example, the cytotoxicity of NK cells can be substantially increased under thermal stress, which might be explained by HSP70 facilitating the upregulated expression of NKG2D, leading to improved recognition and destruction of tumour cells by NK cells[130,131]. Hyperthermia also promotes the differentiation of $CD8^+$ and $CD4^+$ T cells into memory T cells and $T_H$ cells, respectively, leading to long-term tumour-specific immune responses on tumour cell rechallenge in mouse models[132,133].

Nowadays, the main immunotherapies used in clinical cancer therapy are ICIs and cellular immunotherapies such as CAR T cells. The therapeutic indices of these modalities are acceptable, although improvements in the performance of these therapies are important to expand the scope of their application. Heat stimulation alone can facilitate antitumour immunity[134]; therefore, thermal therapies hold great promise to synergize with these clinically approved immunotherapies. Indeed, several clinical trials (either completed or ongoing) have investigated or are exploring the safety and efficacy of a thermal therapy combined with one or more immunotherapies, and some of these studies have already provided promising results (Table 3). For example, the anti-CTLA4 antibody tremelimumab combined with RFA resulted in an objective response rate (ORR) of 26% in 19 patients with advanced-stage unresectable HCCs with disease progression on sorafenib[41]. Progression-free survival at 6 and 12 months was 57.1% and 33.1%, and median time to progression and overall survival (OS) durations were 7.4 months and 12.3 months, respectively. Several patients had shrinkage of non-target lesions following a single round of intrahepatic nidus ablation and administration of tremelimumab, suggesting an immune-sensitizing effect of RFA. Moreover, no clear differences in the incidences of adverse events emerged across patients

**a Radiofrequency ablation**

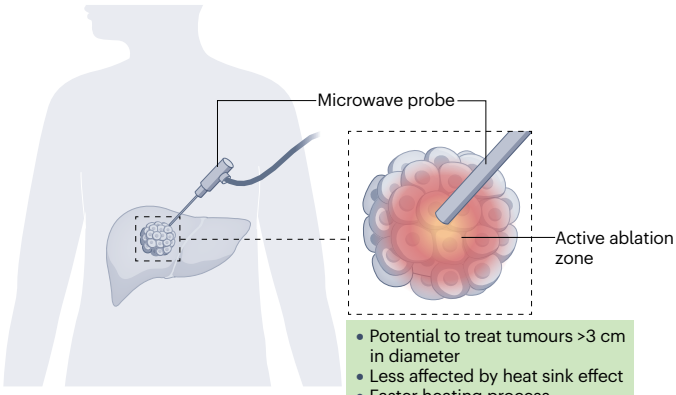



- High rates of complete ablation in tumours (<3 cm)
- Established safety profile
- Majority of lesions reachable

- Heat sink effect in perivascular tumours
- Thermal injury to adjacent tissues

**Indications**
Liver, colorectal, kidney, oesophagus and thyroid cancers, spinal metastases, osteoid osteoma

**b Microwave ablation**

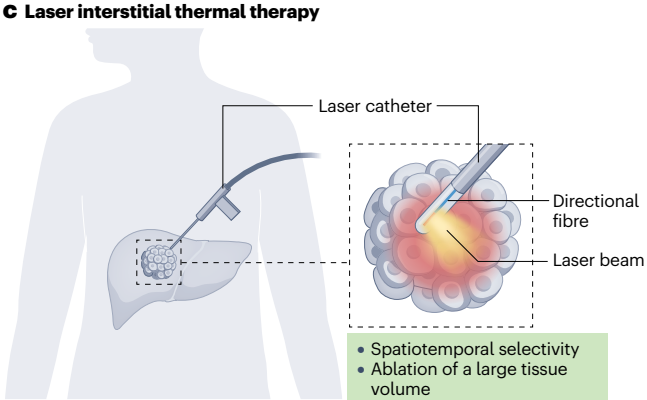



- Potential to treat tumours >3 cm in diameter
- Less affected by heat sink effect
- Faster heating process

- Size of ablation zone harder to predict
- Thermal injury to adjacent tissues

**Indications**
Liver, lung, bone and pancreatic cancers

**c Laser interstitial thermal therapy**

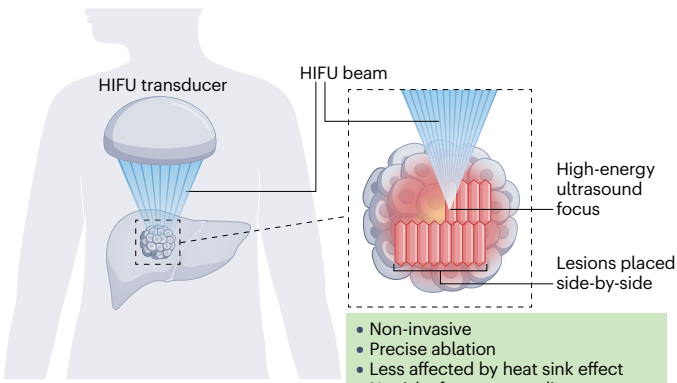



- Spatiotemporal selectivity
- Ablation of a large tissue volume
- Distinct lesion borders

- Limited light penetration
- Low photothermal conversion efficiency of tissues without PTAs

**Indications**
Gliomas, meningiomas, ependymoma

**d HIFU ablation**

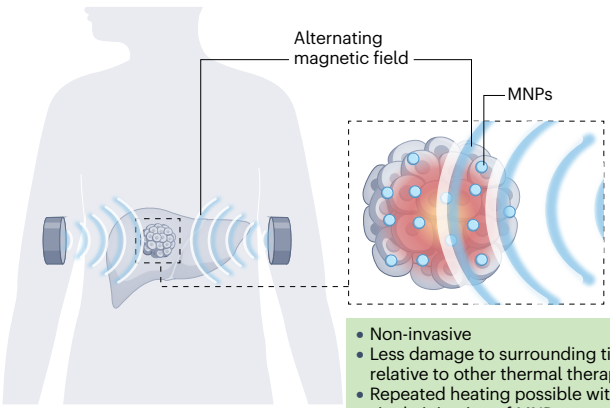



- Non-invasive
- Precise ablation
- Less affected by heat sink effect
- No risk of tumour seeding

- Long treatment time (several hours)
- Ultrasound sonography is obstructed by bone and air-filled viscera

**Indications**
Prostate, breast, desmoid, liver, kidney and pancreatic cancers, osteoid osteoma, uterine fibroids

**e Magnetic hyperthermia**




- Non-invasive
- Less damage to surrounding tissues relative to other thermal therapies
- Repeated heating possible with single injection of MNPs

- Toroidal heating pattern and low magnetic energy absorption
- Highly reliant on MNPs of high concentration

**Indications**
Glioblastoma

Advantages | Disadvantages

**Fig. 2 | Graphical representation of the main thermal therapy modalities.** Several thermal therapies are available and are applied in certain clinical scenarios, each with its own specific characteristics. These include radiofrequency ablation (part **a**), microwave ablation (part **b**), laser interstitial thermal therapy (part **c**), magnetic hyperthermia (part **d**) and high-intensity focused ultrasound (HIFU) ablation (part **e**). MNPs, magnetic nanoparticles; PTAs, photothermal agents.

receiving different doses of tremelimumab. The most common grade 3–4 adverse event was increased systemic aspartate aminotransferase (in 21% of patients)[41]. In another ongoing phase I/II trial involving a similar cohort of 48 patients with advanced-stage HCC, patients received either monotherapy with the anti-PD-1 antibody toripalimab or thermal ablation followed by toripalimab either 3 or 14 days post-ablation. At the latest follow-up cut-off, patients undergoing thermal ablation had ORRs of 37.5% and 31.2%, respectively, which were higher than that of patients receiving toripalimab monotherapy (18.8%). Safety results were also reported, indicating that 75% of patients had at least one any-grade adverse event. Grade 3–4 adverse events occurred in 18.7% of patients[39]. Similarly, in 33 patients with advanced-stage HCC receiving anti-PD-1 antibodies (pembrolizumab or nivolumab) followed by RFA or MWA, the ORR increased from 10% to 24% following thermal ablation; however, whether this finding reflects synergy or a delayed response to immune-checkpoint inhibition remains uncertain. Median progression-free survival and OS durations were 5 months and 16.9 months, respectively[40]. In summary, the safety profile of a thermal therapy–immunotherapy combination appears similar to that of single-agent ICIs. Further investigations of the efficacy of thermal therapy–immunotherapy combinations in patients with HCC should involve comparisons with the current standard-of-care approach.

## Thermal immuno-nanomedicines

On the basis of data described in the previous section, thermal therapy–immunotherapy combinations have the potential to improve outcomes[41,134]. However, ICIs have several limitations, including the risk of immune-related adverse effects and the lack of responses in most patients, both of which remain major challenges for such combinations. For example, in a phase III clinical trial completed in 2019, 609 patients with stage III NSCLC received the anti-PD-L1 antibody atezolizumab; 64% of patients had treatment-related adverse events of any grade and 32% had clinically serious events[135]. Only 18% of patients had an objective response.

With the development of nanotechnology, nanomedicine arises as a promising way to address these limitations owing to several advantages over more traditional therapies, including increased intratumour accumulation, prolonged in vivo circulation time, and the potential for improved safety and/or controlled release of their pharmacological cargoes. At least 20 nanomedicines are currently in clinical use as cancer therapies globally, and 566 clinical trials involving nanomedicines as cancer therapies were conducted between 2016 and 2020 (ref. 136). Some of these agents (such as nab-paclitaxel) had improved efficacy when combined with immunotherapy[14,137,138]. Nanomedicines also have the potential to combine multiple functions in a single platform, including the spatiotemporal synchronized co-delivery of hyperthermia and an immune adjuvant[47,48,139]. Thus, the application of nanomedicines for thermal immunotherapy holds great promise (Fig. 3).

### In situ vaccines

Vaccines have an important role in modern public health. Several different types of vaccines have been developed for various infectious diseases (including live-attenuated vaccines, mRNA vaccines and recombinant vector vaccines), and some of these designs have been applied to the development of therapeutic vaccines for patients with cancer[140–145]. Most available cancer vaccines are designed to promote an immune response to a limited number of antigens rather than to all potential antigens derived from the target tumour,

**Table 3 | Data from trials testing thermal therapy–immunotherapy combinations**

| Trial | Patient characteristics | Intervention | Outcomes |
|---|---|---|---|
| **RFA** | | | |
| NCT01853618 (phase I/II)[41] | 32 patients with HCC not amenable to potentially curative liver transplantation, resection or ablation | Tremelimumab every 4 weeks, subtotal RFA or CA on day 36 | ORR: 26.3% among 19 evaluable patients; 6-month and 12-month PFS: 57.1% and 33.1%, respectively; median OS: 12.3 months; grade 3–4 serum AST increases in 21.8% of patients |
| NCT03695835 (observational)[278] | 27 patients with metastatic solid tumours, including 21 with prostate cancers | In situ cryosurgical lysis of tumour cells followed by intratumoural injections of pembrolizumab, nivolumab or ipilimumab plus sargramostim | ORR: 47% among 19 evaluable patients with prostate cancer; 62% of patients had post-therapy serum PSA reductions of >50%; grade 3–4 adverse events in 19% of patients |
| NCT03939975 (phase II)[40] | 50 patients with advanced-stage HCC with disease progression on sorafenib or who were unable to tolerate sorafenib monotherapy | At least one cycle of pembrolizumab or nivolumab monotherapy; 33 patients (66%) received subtotal RFA repeated up to 4 times | ORR: 24%; median PFS: 5 months; median OS: 16.9 months; clinically serious adverse events in 14% of patients |
| **RFA/MWA** | | | |
| NCT03864211 (phase I/II)[a][39] | 48 patients with advanced-stage HCC with disease progression on at least one systemic therapy | Toripalimab monotherapy (arm A), subtotal ablation of up to 5 lesions plus toripalimab 3 days after ablation (arm B) or toripalimab 14 days after ablation (arm C) | ORR: 18.8% in arm A, 37.5% in arm B and 31.2% in arm C; grade 3–4 TRAEs in 18.7% of patients in arm A and 25.0% in arms B and C, respectively. |

NCT04707547, NCT03101475, NCT02851784 are listed as 'completed' in CinicalTrials.gov, with results unavailable, to the best of the authors' knowledge. AST, aspartate aminotransferase; CA, chemotherapy ablation; HCC, hepatocellular carcinoma; MWA, microwave ablation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; RFA, radiofrequency ablation; TRAEs, treatment-related adverse events. [a]Currently listed as 'ongoing' in ClinicalTrials.gov.

which might explain their limited effectiveness. As described previously, the ICD induced by tumour-ablative thermal therapies causes the release of various tumour-associated antigens (TAAs), which could, if recognized by the immune system, lead to an antitumour immune response capable of suppressing the growth of both primary tumours and their metastases[18]. Thus, TINs could act as an in situ cancer vaccine.

To test this hypothesis, investigators synthesized an amphiphilic polymer, glycol chitosan-graft-polyaniline, and used it to encapsulate the Toll-like receptor 7/8 agonist resiquimod as a nanoparticle-based in situ cancer vaccine[146]. In an acidic TME, this nanoparticle system induced a localized increase in temperature following near-infrared (NIR) laser irradiation. This mild hyperthermia promoted the expression of HSP70 and activation of the immune system, which

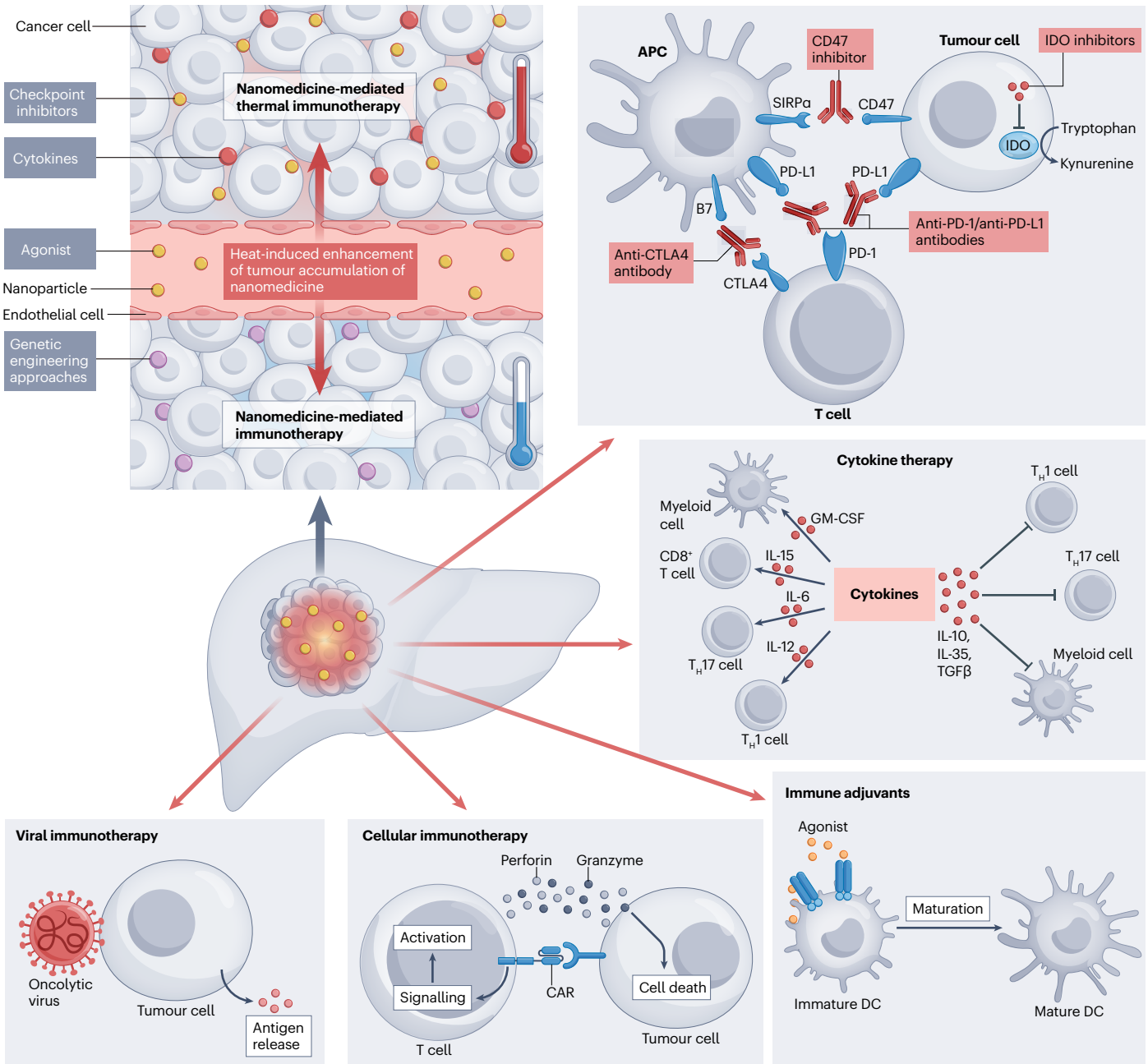



**Fig. 3 | Thermal immuno-nanomedicines.** Nanomedicines for thermal immunotherapy are designed to induce targeted tumour-specific hyperthermia and to synergize with the various clinically approved immunotherapies (including vaccines, immune-checkpoint inhibitors, cellular immunotherapies, oncolytic viruses and cytokine therapies) to further improve their therapeutic efficacy and potentially expand the scope of their application. APC, antigen-presenting cell; CAR, chimeric antigen receptor; DC, dendritic cell; GM-CSF, granulocyte–macrophage colony-stimulating factor; IDO, indoleamine-2,3 dioxygenase; SIRPα, signal-regulatory protein-α; $T_H$, T helper.

synergized with resiquimod to further strengthen antitumour immunity in mouse models with pre-established subcutaneous tumours. Exposure to the TIN resulted in complete tumour regression in 43% of mice; in comparison, monotherapy with either mild hyperthermia or resiquimod delayed tumour growth but failed to induce tumour regression. Cancer cell membrane-coated nanomedicines have attracted considerable research interest as cancer vaccines owing to their selective intratumour accumulation due to homotypic aggregation and the potential to present multiple antigens, thus overcoming the issue of tumour heterogeneity[147–149]. In a hybrid design, bacterial outer membrane vesicles were mixed with cancer cell membranes to formulate a membrane-camouflaged poly(lactic-co-glycolic) acid–indocyanine green (PLGA-ICG) nanoplatform[150]. This nanoplatform features several natural adjuvant components inherited from the parent bacteria as well as cell-surface TAAs from the cancer cells. More importantly, the localized increase in temperature induced by ICG under NIR irradiation could generate supplementary TAAs to further stimulate the immune system. When tested in mouse models of subcutaneous melanoma, this TIN was found to confer an 80% reduction in tumour volume, which is substantially greater than that achieved with monovesicle-camouflaged nanoparticles (30%), indicating that simultaneous PTT substantially improves the antitumour activity of immunotherapy. Future TIN-based cancer vaccines could include additional agents designed to alleviate the immunosuppressive effects of the TME. Elsewhere, investigators prepared a hydrogel loaded with ICG (a photothermal agent) and JQ1 (a BRD4 inhibitor) and tested this approach as post-surgical immunotherapy in mouse xenograft models[151]. This cancer vaccine can be activated and triggered by NIR irradiation for the on-demand release of tumour-specific antigens and JQ1, which can suppress disease relapse by facilitating DC maturation, enhancing cytotoxic T cell infiltration into tumours and inhibiting PD-L1-dependent immune evasion. TIN-based cancer vaccines integrate the ability to generate local hyperthermia and to modulate the immune system for improved antitumour activity and provide a versatile platform for the rational design of more sophisticated therapeutic systems. The combination of hyperthermia and one or more immune adjuvants promotes immune cell infiltration and confers durable antitumour immunity in mouse models, suggesting the release of multiple TAAs from the primary tumour[150,151]. Use of this in situ vaccine approach provides a powerful and personalized method that avoids the need to identify and manufacture TAAs. Although promising, this technology is still currently only being tested in preclinical investigations.

### Immune-checkpoint inhibition

Immune checkpoints are important cell-surface immunoregulatory signalling proteins that can be hijacked to enable cancer cells to evade the immune system[152,153]. Thus, immune-checkpoint inhibition, enabling T cells to recognize and kill cancer cells, is now an important therapeutic modality. Currently, several ICIs, such as those targeting PD-1, PD-L1, CTLA4 or CD47, are used clinically to treat various forms of cancer. Furthermore, agents targeting enzymes with immunosuppressive effects, such as indoleamine-2,3 dioxygenase 1 (IDO1), are an area of considerable research interest[154–157]. Preclinical evidence suggests that combination with hyperthermia further enhances the anticancer activity of these agents.

**CTLA4.** CTLA4 expressed on effector T ($T_{eff}$) cells and $T_{reg}$ cells competes with CD28 for B7 ligands and, when activated, suppresses the activation and growth of $T_{eff}$ cells and the generation of effector memory T ($T_{em}$) cells[158,159]. Thus, inhibition of CTLA4 signalling can restore the activity of $T_{eff}$ cells and facilitate the production of $T_{em}$ cells, promoting antitumour immunity[160]. Data from an increasing number of studies indicate that the anticancer activity of anti-CTLA4 antibodies can be improved by combination with hyperthermia[161–164].

Anti-CTLA4 antibodies have been combined with magnetic hyperthermia and PTT in several preclinical studies. In one example, investigators prepared bullet-shaped $Fe_3O_4$-tipped mesoporous silica magnetic nanoparticles (also known as Janus nanobullets) with a chlorine e6 (Ce6) cytotoxic payload enveloped by a cancer cell-derived membrane. This Janus nanobullet enabled TME-responsive Ce6 release in the presence of an oscillating magnetic field and NIR irradiation, leading to glutathione depletion, reactive oxygen species (ROS) augmentation and magnetic hyperthermia, with evidence suggestive of ICD in mouse xenograft models of breast cancer[161]. Elsewhere, researchers have leveraged the excellent photothermal properties of carbon nanotubes, especially single-walled nanotubes, for targeted thermal therapy. Single-walled nanotubes non-covalently modified with polyethylene glycol (PEG) were constructed and used for PTT in combination with anti-CTLA4 antibodies, resulting in a significantly longer time to cancer recurrence in mouse models of lung metastases. This approach facilitated $T_{eff}$ cell expansion while also substantially reducing the number of $T_{reg}$ cells in distant lesions[105].

**PD-1–PD-L1.** The PD-1–PD-L1 signalling pathway is another important immune checkpoint. PD-1 is predominantly expressed on activated T cells and its ligands, PD-L1 and PD-L2, are expressed on antigen-presenting cells and some cancer cells, which might explain the adaptive immune resistance, or immune evasion, seen in many cancers[165]. Worldwide, at least ten different anti-PD-1 or anti-PD-L1 antibodies are in clinical use for the treatment of a wide range of cancers, including NSCLC and melanoma[166,167]. As discussed previously, local hyperthermia promotes immune cell infiltration and induces ICD; thus, similar to anti-CTLA4 antibodies, thermal therapies are also likely to synergize with anti-PD-1 and anti-PD-L1 antibodies. To test this hypothesis, investigators prepared an injectable lipid gel loaded with PTAs and anti-PD-L1 antibodies. This temperature-sensitive lipid gel underwent phase transition and released the anti-PD-L1 antibody simultaneously with hyperthermia, which resulted in impaired tumour growth and T cell recruitment to the tumour[48]. Similarly, when combined with anti-PD-L1 antibodies, ferrimagnetic vortex-domain iron oxide nanorings capable of magnetic hyperthermia impaired the growth of non-target lesions following thermal ablation of a target lesion in a mouse xenograft model. This approach conferred marked increases in CD3 and CD45 levels (indicating increased T cell and haematopoietic cell counts) and a considerable reduction in myeloid-derived suppressor cell levels in tumours distant to the target lesion, suggesting activation of systemic immunity[168].

As discussed above, combining anti-PD-1/anti-PD-L1 antibodies with hyperthermia is the most widely used immunotherapy–thermal therapy combination strategy[169,170]. However, as mentioned previously, the systemic administration of these antibodies as monotherapies typically results in limited response rates and risk of immune-related adverse effects[171]. To address this problem, gene-editing or gene-silencing technologies could be utilized to achieve persistent inhibition of PD-1–PD-L1 signalling. Small interfering RNAs (siRNAs) theoretically enable the expression of any specific gene to be silenced by post-transcriptional mRNA degradation, providing a powerful technology that could potentially be adapted for cancer therapy[172,173]. However, clinical approaches involving siRNA are often impaired by rapid

enzymatic degradation and an inability to penetrate cell membranes; therefore, most siRNA-based therapies require a targeted delivery system. An example is provided by patisiran, an siRNA-containing lipid nanoparticle approved by the FDA in 2018 for the treatment of peripheral nerve disease caused by hereditary transthyretin-mediated amyloidosis in adults. Delivery of the siRNA using a lipid nanoparticle improved the in vivo stability and enabled selective accumulation in the liver owing to surface adsorption of apolipoprotein E (ApoE)[174]. Other promising siRNA-containing nanoparticles currently in development include siRNA-GalNAc conjugates and Dynamic PolyConjugates, which involve the conjugation of siRNAs with specific ligands or polymers, respectively[175]. Among other possibilities, TINs could provide the delivery vehicle for PD-L1-silencing siRNAs. In a preclinical study, gold nanoparticles capable of both delivery of PD-L1 siRNA and PTT were prepared and shown to suppress the proliferation of cancer cells in mouse xenograft models through PD-L1 knockdown and hyperthermia following NIR laser irradiation[176]. The CRISPR–Cas9 system provides an alternative target-specific gene-editing tool[177,178]. Since its discovery in 2010, CRISPR–Cas9 has been widely used for in vitro gene editing in experimental models, and this approach theoretically has tremendous potential as a treatment of various diseases owing to its versatility and simplicity[179–182]. As a powerful gene-editing tool, this technique creates considerable ethical and safety concerns, especially when used in applications such as in vivo germline gene editing; nonetheless, considerable public support and research interest exist in the therapeutic application of this technology. Early proof-of-principle data supporting the in vivo use of CRISPR–Cas9 technology in patients come from a phase I study in which six patients with hereditary transthyretin-mediated amyloidosis and polyneuropathy received a lipid nanoparticle formulation containing RNA encoding Cas9 and a guide RNA targeting *TTR*. Early results showed durable suppression of the target gene (mean reduction in TTR protein levels of 52%) after a single dose with only mild (grade 1) adverse events[183]. CRISPR–Cas9 has been applied to the development of TINs designed to also disrupt *PD-L1*. In a preclinical study, investigators fabricated supramolecular cationic-gold nanorods loaded with plasmids encoding *Cas9* and a single guide RNA targeting PD-L1 downstream of a heat-sensitive promotor, which potentially reduces the risk of off-target events compared with untargeted expression[184]. Upon NIR II (1,000–1,700 nm) laser irradiation, the mild hyperthermia generated by PTT increased the local temperature to 42 °C, enabling transcriptional activation of Cas9 and suppression of PD-L1, which promoted T cell infiltration and an expansion of $T_{em}$ cells, thus providing systemic antitumour immunity that delayed the growth of distant lesions in mouse xenograft models.

**CD47.** CD47 is expressed on different types of cancer cell, such as non-Hodgkin lymphoma, acute myeloid leukaemia, glioblastoma, ovarian, breast, colon, bladder, hepatocellular, and prostate cancers, and binds to signal-regulatory protein-α (SIRPα) on macrophages to suppress phagocytic function, acting as a 'do not eat me' signal[185]. Anti-CD47 antibodies have been shown to be well tolerated in a phase I clinical trial involving 62 patients with advanced-stage cancers[186]. In another phase Ib study, the combination of an anti-CD47 antibody with rituximab showed promising activity in patients with relapsed and/or refractory non-Hodgkin lymphoma without the emergence of any clinically significant adverse events[187]. Several more clinical trials involving anti-CD47 monoclonal antibodies as cancer treatments are currently ongoing (NCT02216409, NCT02367196, NCT02447354 and NCT02488811)[136–138]. Data from several studies also demonstrate that anti-CD47 antibodies facilitate DC activation and T cell priming[188]. Similar to the experience with other ICIs, concurrent hyperthermia potentiates the antitumour activity of anti-CD47 antibodies in preclinical models[189–192]. An example of this effect is provided by a hybrid therapeutic nanocarrier fusing CD47-overexpressing exosomes with ICG and imiquimod-loaded thermoresponsive liposomes[190]. This approach promoted DC maturation and the lethality of $CD8^+$ and $CD4^+$ T cells and macrophages in a mouse xenograft model.

### IDO1 inhibition

IDO1 catalyses the metabolism of tryptophan, which is the first and rate-limiting step in the kynurenine synthesis pathway[193–196]. This enzyme enables cancer cells to evade the immune system through two main mechanisms: tryptophan depletion, which can suppress the activation and proliferation of $T_{eff}$ cells, and kynurenine production, which is cytotoxic to T cells and NK cells but promotes the proliferation of $T_{reg}$ cells and $T_H17$ cells. Thus far, more than 10 different IDO1 inhibitors have been tested in preclinical studies or clinical trials, albeit without any notable success in phase III studies[197]. Several studies have focused on combining IDO1 inhibitors with thermal therapy in an attempt to improve the efficacy of these agents[198,199]. Ultrathin microporous polymer nanosheets conjugated to a NIR-sensitive semiconducting polymer and coated with the IDO1 inhibitor 1-methyltryptophan (1-MT) were used to simultaneously induce ICD and inhibit IDO1 activity[200]. This system enables the concurrent generation of hyperthermia, ROS and oxygen, which alleviates tumour hypoxia and elicits the generation of ROS. After intravenous administration and NIR laser irradiation, mice injected with TINs had a substantial reduction in tumour growth, whereas mice injected with the nanosheet without 1-MT plus irradiation had moderate inhibition of tumour growth and non-irradiated mice had minimal inhibition of tumour growth. Our group synthesized a thermal-sensitive nitric oxide (NO) donor poly(acrylamide-co-acrylonitrile-co-vinylimidazole)–S-nitrosothiol pendant copolymer with an upper critical solution temperature (42.1 °C in a weakly acidic TME), which was used to prepare an erythrocyte membrane-camouflaged nanoparticle with the NIR II photothermal agent IR1061 and with 1-MT as a payload[139]. The hyperthermia at the tumour site induced by PTT elicited ICD but also triggered the release of 1-MT and NO to regulate the kynurenine metabolic pathway and alleviate hypoxia, respectively[201–203]. This multifunctional nanomedicine promoted the recruitment of cytotoxic T cells to the tumour site and suppressed PD-L1 expression and $T_{reg}$ cell proliferation, while polarizing tumour-associated macrophages towards an M1 phenotype, collectively reversing immunosuppression in hypoxic and immune-cold tumours in a mouse xenograft model. In addition to synergy between hyperthermia and IDO1 inhibition, the controlled release of NO from TINs could remodel the TME and further enhance antitumour activity.

### Cellular immunotherapy

The aim of cellular immunotherapy is to isolate immune cells, either from patients with cancer or from HLA-matched or potentially even unmatched individuals, genetically modify and/or expand the cells in vitro, and then infuse them back into the patient to directly kill the tumour and/or promote antitumour immunity[204]. Several different forms of cellular immunotherapies exist, including tumour-infiltrating lymphocytes, TCR-engineered T cell and CAR T cell therapies, and genetically modified and/or expanded NK cell or DC-based immunotherapies[205–207]. Currently, five different CAR T cell constructs are approved for patients with B cell malignancies (idecabtagene vicleucel, lisocabtagene maraleucel, tisagenlecleucel, brexucabtagene autoleucel

and axicabtagene ciloleucel) and two for multiple myeloma (idecabtagene vicleucel and ciltacabtagene autoleucel)[208]. Anti-CLL1 CAR T cells are also approved by the FDA as orphan drugs for patients with acute myeloid leukaemias[209]. Various other constructs are also currently in the late stages of clinical testing, including relmacabtagene autoleucel as a second-line therapy for patients with diffuse large B cell lymphoma[210]. Cellular immunotherapies are clearly effective in patients with advanced-stage B cell malignancies; however, limited infiltration of the re-infused cells is often seen in patients with solid tumours receiving experimental CAR T cells and this restricts the broader use of cellular immunotherapies. Ablative hyperthermia has the potential to damage or destroy extracellular matrix and other TME components, thus removing a major barrier to infiltration[211–214]. The ensuing ICD could also stimulate the production of pro-inflammatory cytokines and chemokines, and promote the recruitment of both adoptive immune cells and potentially native immune cells to non-ablated lesions[214,215]. For example, adoptive transfer of gp100-specific pmel T cells following hollow gold nanoshell-mediated PTT enables antitumour activity against non-ablated lesions as demonstrated by the suppression of lung metastases in a mouse xenograft model of melanoma[216]. A similar approach was investigated using PTT to improve the antitumour activity of CAR T cells in a mouse xenograft model of melanoma[214]. In this study, ICG-loaded PLGA nanoparticles were used to induce local hyperthermia following laser irradiation leading to ICD of cancer cells, resulting in the destruction of the extracellular matrix, immune cell infiltration and increased tumour-specific expression of several chemokines and cytokines. T cells genetically engineered to express a CAR targeting chondroitin sulfate proteoglycan 4 (CSPG4), a specific antigen overexpressed in glioblastoma and melanoma, were infused 2 h after laser irradiation. The tumour-specific accumulation of anti-CSPG4 CAR T cells was increased in mice previously exposed to PTT, resulting in substantial suppression of tumour growth up to 20 days following CAR T cell administration. These preclinical data suggest that combining mild hyperthermia with CAR T cell infusion enhances the antitumour activity of CAR T cells. Mild hyperthermia induced by NIR light not only inhibits the growth of cancer cells but can also enable the controlled in vivo generation and/or release of therapeutics. To further assess this possibility, investigators constructed and screened panels of synthetic thermal gene switches containing the combinations of heat-shock elements and core promoters to identify constructs that respond to mild hyperthermia[217]. Under photothermia generated using PTT (40–42 °C), these heat-responsive promotors are able to control the production of several immunostimulatory genes, including those encoding bispecific T cell engagers and IL-15 superagonists, with antitumour activity observed in mouse models of antigen-negative tumours. Elsewhere, biocompatible electrospun nanofibres embedded with light-sensitive iron oxide nanoparticles were used to promote the photo-activated in vitro permeabilization of T cells to CRISPR–Cas9 ribonucleoprotein complexes and siRNAs targeting PD-1 (ref. 218). This strategy did not affect the proliferation or phenotype of the engineered T cells, with antitumour activity similar to that observed with PD-1-expressing CAR T cells plus anti-PD-1 antibodies.

### Cytokine-based therapies

Cytokines are a category of signalling molecules that includes interferons, chemokines, lymphokines and interleukins with an essential role in regulating the proliferation and activation of immune cells[219]. Approximately 200 different cytokines have been identified as having roles in cell signalling and several, such as IL-7 and IL-12, are currently being tested in clinical and preclinical studies[220,221]. However, systemic administration of cytokines as monotherapies is usually associated with dose-limiting toxicities, which hinders the use of unmodified cytokines as cancer therapies[222]. Among other approaches, researchers have attempted to use nanotechnology to improve the safety, bioavailability and therapeutic efficacy of systemically administered cytokines. An early example of a nanomedicine designed for targeted delivery of a cytokine payload is provided by CYT-6091, a PEGylated colloidal gold nanoparticle with TNF conjugated to its surface. This method of delivery avoids hypotension, which is a dose-limiting toxicity associated with unmodified TNF[223]. Two phase I clinical trials testing the safety and tolerability of CYT-6091 have been completed (NCT00356980 and NCT00436410) and a clinical trial agreement on a phase II study has been signed between the manufacturer and the US National Cancer Institute[224,225]. The rationale for combining these two modalities is based on the ability of hyperthermia to elicit ICD and promote transfection with cytokine-encoding plasmids, leading to the localized release of cytokines capable of TME remodelling. In one approach, protamine-modified superparamagnetic iron oxide nanoparticles capable of magnetic hyperthermia were combined with TNF-encoding plasmids[226]. This nanoparticle demonstrated robust transfection efficiency, possibly assisted by the elevation of temperature created by the alternating magnetic field, with promising synergistic antitumour activity in a mouse xenograft model of HCC. In another approach, CuS-$SiO_2$ nanoparticles were conjugated with positively charged poly((2-dimethylamino)ethyl methacrylate), forming complexes with negatively-charged IL-12-encoding plasmid DNA[227]. Under NIR II irradiation, hyperthermia induced by CuS-$SiO_2$ significantly improved the efficiency of transfection, leading to improved IL-12 release and antitumour activity beyond the target lesion. In the bilateral B16F10 mouse xenograft model used, this TIN inhibited the growth of tumours located close to the injection site and suppressed distant lesions within the same mouse, suggesting the emergence of an abscopal effect.

### Oncolytic viruses

Oncolytic viruses are a novel immunotherapy modality involving the use of either naturally occurring or genetically modified viruses to selectively infect and eliminate cancer cells via ICD[228,229]. Thus far, three oncolytic viruses have been approved for clinical use globally: H101 for head and neck cancer in China; talimogene laherparepvec for melanoma in the USA and Europe; and teserpaturev for malignant glioma in Japan[230,231]. At least 10 other oncolytic viruses are currently being tested in clinical trials. In an early attempt to explore the antitumour activity of oncolytic viruses in combination, investigators combined viral oncolysates obtained from individual patients with autologous DCs with modulated electrohyperthermia, which involves selective heating of the extracellular matrix of malignant tissues[232]. In this approach, the immune system of patients is pre-conditioned via injection of an avian Newcastle disease virus and hyperthermia using a radiofrequency of 13 MHz. This step is followed by the administration of autologous DCs exposed to viral lysates obtained by exposing the patient's tumour cells to the Newcastle disease virus in vitro. Preliminary investigations indicate that this approach confers a median OS duration of 30 months in a retrospective cohort of 10 patients with newly diagnosed glioblastoma.

## Future prospects and challenges

On the basis of the available preclinical data, TINs combining thermal therapies and immunotherapies have the potential to improve therapeutic efficacy. The data suggest two main mechanisms of action of

TINs: relieving the immunosuppressive effects of the TME and promoting antitumour immunity via ICD. Thus far, approaches combining these two modalities in a single nanoparticle have not been investigated in clinical trials and several challenges continue to hinder clinical translation.

Firstly, many thermal therapies, including TINs, are affected by a common problem, known as the 'heat-sink effect' or convective cooling, which refers to heat being carried away from the target via the circulation, thus compromising attempts to increase only the local temperature[83]. For RFA in particular, this effect creates an active heating zone that is limited to several millimetres surrounding the tip of the applicator. Heat conduction has an important role in expanding the heating area, which explains the greater susceptibility of this technique to the heat-sink effect compared with other thermal therapeutic modalities[233]. Moreover, the need for homogenous hyperthermia across the entire target lesion creates a further clinical challenge. The deposition of energy during interstitial heating is limited to the close proximity of the probes owing to the line/point nature of interstitial heat sources. As a result, multiple small applicators must be arranged and spaced 1–2 cm apart in order to offset heat loss and cover the entire target lesion, which complicates both clinical operation and ablation zone prediction. Therefore, a trend towards the design of more advanced applicators that provide greater spatial control of energy deposition to ensure ideal temperature distributions across the target tumours while sparing the neighbouring non-malignant tissues is currently emerging. Regardless of these limitations, most TINs currently in preclinical development are activated by lasers for various reasons. Photothermal activation is an appealing method that enables the precise, targeted activation of TINs. Furthermore, lasers are more amenable to laboratory experiments involving small animals relative to other possible methods of TIN activation. However, the limited tissue penetration depth associated with optical activation (restricted to within a few centimetres of the skin surface) impairs the widespread implementation of this approach. Endoscopes equipped with optical fibres designed to deliver light to deep tissues have the potential to address this issue, which would considerably improve the potential for clinical implementation. In this regard, low-temperature-sensitive, liposome-encapsulated nanobubbles have already been demonstrated to enhance the performance of HIFU ablation[234,235], and this approach has the potential to enable localized activation of TINs.

Precise control of temperature is another major challenge associated with the use of TINs. The ICD induced by hyperthermia is highly dependent on achieving an optimal temperature, which means the 'more is better' paradigm might be inappropriate for hyperthermia designed to promote the efficacy of immunotherapy[236]. Furthermore, the higher temperatures required for the thermal ablation of tumour cells might damage non-malignant tissues, including immune cells. This approach can also restrict intratumoural blood flow and cause the tumour to form a barrier that prevents immune cell infiltration and immune induction[237]. However, owing to the disordered geometry and seemingly random location of the tumour blood vessels, uniform heating of an entire tumour is often difficult to achieve. Although various thermometry techniques based on different imaging modalities (such as MRI or photoacoustic imaging) have been applied clinically, each method still has certain limitations[238,239]. For example, hard-wire thermistor or thermocouple-based sensors are prone to measurement errors arising from electromagnetic interference, which might introduce artefacts on MRI images, leading to inaccurate temperature monitoring. Photoacoustic imaging can also provide relative temperature measurements; however, obtaining accurate measurements of absolute temperature without understanding the baseline temperature is challenging, particularly in deep tissues with unknown optical and acoustic properties. Owing to strong light attenuation in biological tissues, photoacoustic imaging can only achieve sufficient contrast from endogenous chromophores at tissue depths of <4 cm (ref. 240). Temperature monitoring is essential to precisely control the thermal conditions of the tumour and enable optimal treatment efficacy with minimal adverse effects; thus, an urgent need exists to improve the technology used for heating and temperature monitoring.

A number of different immunotherapies are currently available. Therefore, how best to select the most appropriate immunotherapy for use in combination with a specific thermal therapy and/or incorporation into TINs in order to maximize therapeutic efficacy remains a major challenge. The rapid development of artificial intelligence (AI) technology provides one possible solution to this problem. In addition to the development of new treatment methods and drugs, the massive amount of medical data available can be analysed using big data analysis and AI technology to achieve the goal of personalized medicine[241–243]. For example, IBM, in collaboration with Memorial Sloan Kettering Cancer Center, designed an AI assistant decision-making system, named Watson for Oncology (WFO)[244]. This system was trained for >4 years based on the national comprehensive cancer network (NCCN) guidelines and >100 years of treatment experience and is designed to suggest the optimal therapeutic schedule for each individual patient. Thus, once a larger body of clinical data on the performance of thermal therapy–immunotherapy combinations, including TINs, becomes available, such approaches could be used to analyse these data and identify predictors of therapeutic efficacy that enable the most appropriate thermal immunotherapy protocol to be recommended on an individual basis.

Meanwhile, despite the impressive outcomes that have been achieved with TINs in preclinical studies, the clinical application of such nanomedicines remains in the proof-of-concept phase and has some limitations in clinical translation. Firstly, the enhanced permeability and retention (EPR) effect has long been believed to be an important mechanism for the accumulation of nanomedicines in tumour tissues. However, the significance and even the existence of the EPR effect in solid tumours in patients is becoming a controversial topic[245]. Emerging evidence suggests that nanoparticles are able to enter solid tumours through mechanisms more complex than previously thought, potentially going beyond simple extravasation through gaps in the endothelial lining. For example, a recent report demonstrated that the EPR effect might not be the major underlying mechanism of nanoparticle extravasation and that active transcytosis also contributes to the tumour-specific accumulation of nanoparticles[245,246]. Therefore, innovative strategies designed to enhance the tumour-specific accumulation of nanoparticles will be needed to facilitate the clinical translation of nanomedicines. Possible strategies include the use of physical methods such as hyperthermia, radiotherapy and ultrasonography, all of which are able to increase vessel perfusion and permeability[247–249]; alternatively, pharmacological strategies, including agents targeting VEGFR signalling and those that generate nitric oxide, can normalize the tumour vasculature and thus promote the tumour-specific accumulation of nanomedicines[203,250–252]. Furthermore, the addition of active targeting ligands, including antibodies, peptides and aptamers, provides a complementary strategy designed to increase the accumulation and retention of nanoparticles in tumours. However, despite a phase II clinical trial of BIND-014, a docetaxel-containing nanoparticle

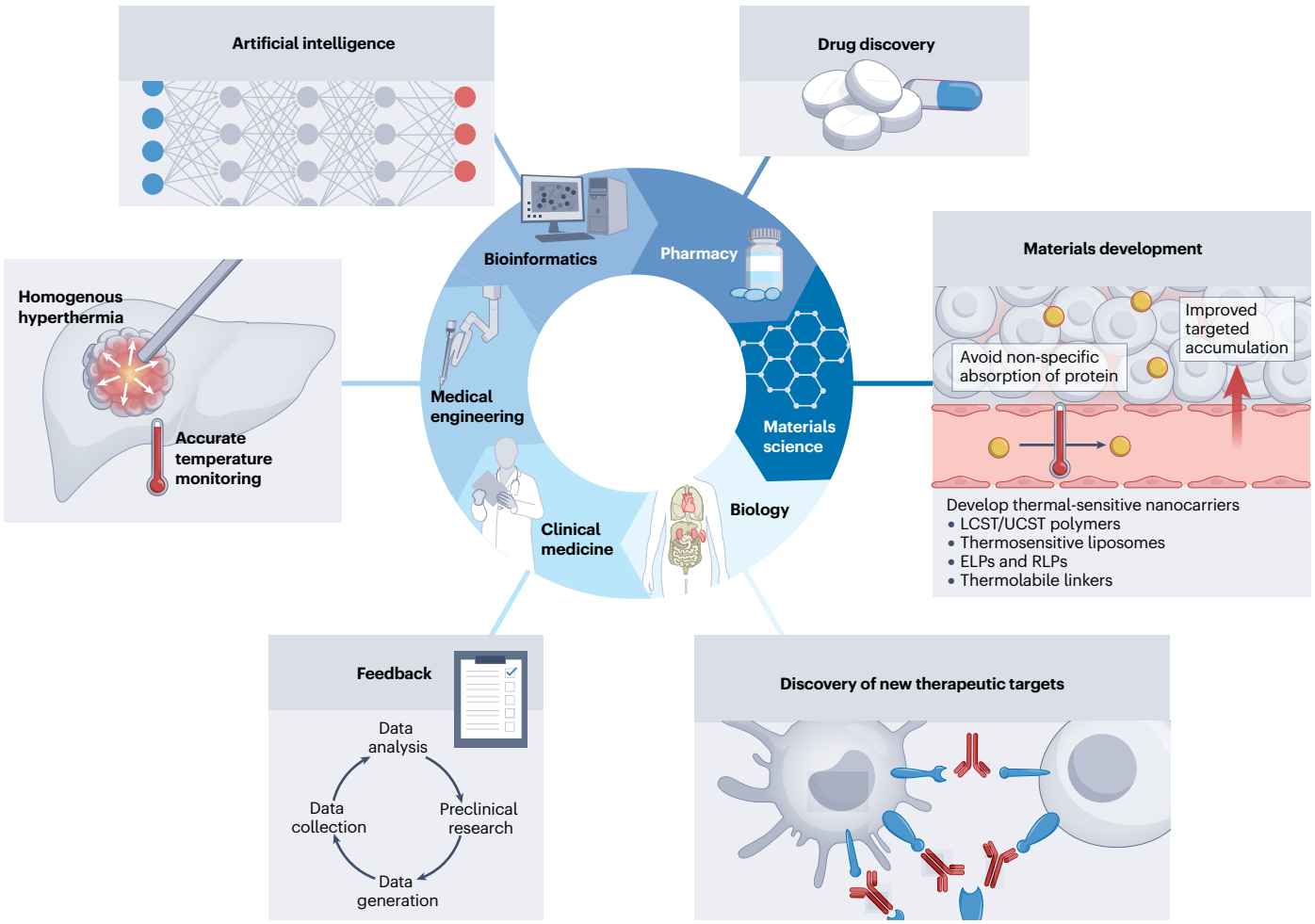



**Fig. 4 | Future development of thermal immuno-nanomedicines driven by a multidisciplinary team.** The clinical translation of thermal immuno-nanomedicines from promising preclinical candidates to approved therapies will require groups of experts, including materials scientists, biologists, oncologists, medical device engineers and even bioinformatics specialists to collaborate as part of a multidisciplinary team to overcome the various challenges associated with the development of nanomedicines that combine the antitumour efficacy of hyperthermia and immunotherapy while minimizing the risks of adverse events. ELPs, elastin-like polypeptides; LCST, lower critical solution temperature; RLPs, resilin-like polypeptides; UCST, upper critical solution temperature.

targeted to prostate-specific membrane antigen (PSMA) in men with prostate cancer, no targeted nanomedicines have been approved for clinical use[253]. Several potential reasons exist for the largely disappointing results seen with nanomedicines in clinical trials; one of the major problems is the protein corona that forms around the surface of nanoparticles upon exposure to biological fluids[254,255]. Nanoparticle surfaces are usually modified with hydrophilic polymers (such as PEG or zwitterionic ligands) to avoid interactions with the biological environment. Nonetheless, the non-specific absorption of proteins to form the protein corona has proven difficult to avoid, and this effect might mask surface-targeting ligands and/or trigger immunological recognition, leading to the rapid clearance of nanomedicines and/or adverse immune reactions.

Ultimately, outside of the current challenges associated with the use of nanomedicines, thermal therapies and/or immunotherapies, combining these modalities together in the same platform creates several new challenges. Firstly, although various TINs have been prepared in labs, the scale-up of TIN production remains challenging. TIN preparation processes, including materials synthesis, encapsulation of therapeutic agents and product purification, typically lead to difficulties in reproducibility and quality control. Furthermore, combining different modalities not only potentially improves the capacity to kill cancer cells but might also increase the risk of adverse events. Hence, improving efficacy without a simultaneous increase in the incidence of adverse events is an important challenge. To achieve this goal, the dose ratio of different therapeutic agents, the power of thermal therapy devices, the choice of more biocompatible materials and the design of TINs must all be optimized to avoid overlapping toxicities and to maximize any synergistic therapeutic effects. Currently, most data on the performance of TINs are from preclinical studies involving mouse models. Therefore, these TINs should be tested in more complex animal models that better reflect the human immune system, which would enable the formulation of more effective TINs and the development of more precise treatment plans.

## Conclusions

Overall, we conclude that developing more effective TINs requires collaboration among multidisciplinary teams of experts, including materials scientists, biologists, oncologists, medical device engineers and even bioinformatics specialists, to fully understand the mechanisms of action of hyperthermia-synergized immunotherapies, develop more effective combination platforms, and manufacture more effective heating and temperature monitoring devices. Addressing these points could further improve the performance of nanomedicines (Fig. 4). Various challenges currently impair both the development of more effective TINs and their clinical translation. Nonetheless, several reasons exist to anticipate that nanomedicines combining hyperthermia and immunotherapy will ultimately provide safe and effective cancer therapies.

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## Author contributions

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## Competing interests

The authors declare no competing interests.

## Additional information

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