Translational Oncology 27 (2023) 101565

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Nanoscale biomaterials for terahertz imaging: A non-invasive approach for early cancer detection

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ARTICLE INFO

Keywords:
Nonionizing terahertz medical imaging
Cancer diagnosis
Early detection
Nanoparticle
Contrast agent

ABSTRACT

Terahertz (THz) technology is developing a non-invasive imaging system for biosensing and clinical diagnosis. THz medical imaging mainly benefits from great sensitivity in detecting changes in water content and structural variations in diseased cells versus normal tissues. Compared to healthy tissues, cancerous tumors contain a higher level of water molecules and show structural changes, resulting in different THz absorption. Here we described the principle of THz imaging and advancement in the field of translational biomedicine and early detection of pathologic tissue, with a particular focus on oncology. In addition, although the main forte of THz imaging relies on detecting differences in water content to distinguish the exact margin of tumor, THz displays limited contrast in living tissue for *in-vivo* clinical imaging. In the last few years, nanotechnology has attracted attention to aid THz medical imaging and various nanoparticles have been investigated as contrast enhancements to improve the accuracy, sensitivity, and specificity of THz images. Most of these multimodal contrast agents take advantage of the temperature-dependent of THz spectrum to the conformational variation of the water molecule. We discuss advances in developing THz contrast agents to accelerate the advancement of non-invasive THz imaging with improved sensitivity and specificity for translational clinical oncology.

Introduction

Medical imaging techniques have been vastly employed and prevailed in healthcare as the key component of precision medicine to enhance diagnosis accuracy and improve treatment outcomes of patients with various medical conditions [1]. There are various conventional medical imaging methods naming: X-ray radiography, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), ultrasound imaging, and thermography that differently examine anatomy and/or physiology of the whole human body or specific tissue [2]. Each of these fashions has its applications with a variety of complexity, safety concerns, image quality, and resolution. Choosing proper examinations is always a tradeoff between their benefits and risks.

Unfortunately, most medical imaging devices deliver a certain amount of ionizing radiation over time which is associated with inherent health problems, especially for children and pregnant women. Furthermore, enhancing the medical imaging quality also requires more dosage of the radiation or time, which in turn induces a higher risk to the patient. During the last decade, numerous research has been done in biomedical imaging to develop new imaging modalities to reduce medical imaging risks and unnecessary radiation exposure while increasing imaging quality and diagnostic precision [3].

With the advancement of science and technology, terahertz (THz) radiation has recently attracted much attention as an uncharted territory that could open a window of opportunity in medical imaging for various applications, including non-invasive cancer diagnosis. THz imaging employs non-ionizing radiation to examine pathological organs and more precisely distinguish tumoral borders versus intact tissue without causing further health concerns. However, THz imaging suffers from limited sensitivity and spatial resolution. In addition to tremendous progress in imaging modalities, the development of contrast agents is another appealing area to improve quality and resolution images and enhance interpretability for more precise medical diagnosis.

Up to date, many reviews have discussed different imaging techniques and contrast enhancements. However, through this review, for the first time, we discussed THz imaging specifically for cancerous tissue detection and the development of contrast agents to improve the quality

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https://doi.org/10.1016/j.tranon.2022.101565
Received 8 July 2022; Received in revised form 12 September 2022; Accepted 9 October 2022

of THz imaging. This interdisciplinary review provides a cornerstone and helps researchers in the field to facilitate the progress of the THz technique for translational oncology.

Principle of terahertz technology

THz radiation is applied to submillimeter electromagnetic (EM) wavelength in a range between 3000 to 30 μm with a correspondence frequency of 100 GHz (0.1 THz) to 10 THz, which is situated between millimeter-wave and infrared bands in the EM spectrum (Fig. 1) [4–6].

THz radiation has gained enormous attention in various fields such as physics, chemistry, material science, electronic industry, communication, quality control, medicine, and biosensing [7–9]. Diverse and tremendous applications of THz technology for sensing and imaging stem from a plethora of water absorption bands and rotational molecular resonances in the THz spectrum [10]. Furthermore, compared to other imaging modalities with lower frequencies, the smaller wavelength of THz waves enables remarkable precision for high-resolution imaging [10]. This technique also benefits from remote inspection of surface topography and physical and chemical characterizations of material [11].

The THz beam can probe living tissue and biological materials without any adverse impact due to its low photon energy [12]. However, THz has hitherto remained uncharted for clinical applications due to the bulky and high-power required equipment. For example, using photoconductive antennas as THz transceivers necessitate high-power femtosecond lasers to generate THz pulses and compensate for the propagation loss to have sufficient power on the receiver side. Specifically, the high water content and THz wave absorptivity in the biological specimen require strong radiated THz waves and high-sensitivity receivers, making these THz transceivers inadmissible for clinical application [10,13]. Besides high-power generators, THz technology also requires efficient detectors [14].

Recent advances in developing electronic THz sources and detectors, using nanotechnology, metamaterials, microfabrication technology, and advancement of complementary-metal-oxide-semiconductor (CMOS) devices for constructing integrated circuit (IC) chips have provided a great opportunity to more efficiently exploit the electromagnetic radiation spectrum in the range of THz and expand this technology for biosensing and medical imaging [5,15–17]. Many researchers, including our group, have vastly focused on designing and fabricating fully integrated systems on silicon to produce an energy-efficient and portable THz imaging system. The Frequency-Modulated Continuous-Wave (FMCW) radar is among the best candidates for THz imaging systems. THz FMCW radar arrays offer intermediate-frequency signals in the order of MHz at the receiver, simplifying data processing and providing an excellent opportunity for a real-time THz imaging system to depict dynamic 3D images. THz imaging systems can generally be classified based on transmission or reflection-based geometry (Fig. 2). In reflection-based imaging, the transmitter (emitter) and receiver (detector) are on the same side of the sample, and the imager works based on the interaction of the evanescent electromagnetic waves with the specimen, which provides a decent THz signal at the receiver. However, the THz beam should pass through the sample in the transmission imaging systems, making this method impractical for biomedical imaging applications because of the high THz wave absorption of the biological samples. Therefore, the reflective approach is the primary choice for THz medical imaging [10].

Due to vast advancements in THz technology besides non-destructive sampling and non-invasive sensing of this technique, THz application has been recently expanded for biomedical imaging, biological sensing, and pharmaceutical characterization applications [6].

THz spectroscopy is commonly used in biomedicine to study, recognize and classify biomolecules based on their THz spectrum characteristics [4]. Proteins, DNA, and RNA components can interact with EM waves and show distinct transmittance spectral in the frequency range of 0.4–5.8 THz, which can be employed to distinguish these molecules [18]. THz has also emerged as a novel and expanding technique that provides a more accurate analytical tool than traditional X-ray diffraction and liquid chromatography. THz spectroscopy offers higher sensitivity even at low temperatures to evaluate pharmaceutical ingredients and distinguish similar molecular species and structures of drug molecules in a wide range of molecular weight, making it an unprecedented tool to accurately detect impurities in pharmaceutical products [19]. Non-invasive and non-destructive THz spectrometers benefit from high frequency and resolution besides the strong absorption of targeted drug crystals based on their THz spectrum characteristics [20].

Terahertz application for medical imaging

Early detection of disease is of great interest in modern medicine. Medical imaging technologies are essential for providing anatomical and physiological information for preventive, predictive, early diagnosis, screening, and individualized treatment. One of the crucial challenges in medical imaging is to precisely delineate the margin between healthy and diseased tissue [21–24]. Existing medical imaging such as CT and MRI provide minimal-invasive images; however, these macroscopic images have limited resolution and specificity to acquire detailed structural and biological data. To improve accuracy, they mostly should be validated with additional anatomical and clinical information or histopathological report from biopsy specimens [25,26].

Unrivaled properties of THz convinced bioengineers and medical scientists to develop THz medical imaging to bridge the gap between macroscopic and microscopic (structural and functional) imaging so that the precise margins of cancers can be delineated [13]. Furthermore, there is considerable concern about these diagnosis techniques that employ ionizing radiation for medical examination [27].

Frequent ionized imaging of sensitive patients such as pregnant women and children may impose detrimental effects on healthy organs and increase the risk of cancer. To minimize the risk of exposure National Council on Radiation Protection and Measurements (NCRP) stated to keep radiation doses as low as reasonably achievable (ALARA) for medical imaging. Based on the ALARA principle, it is highly

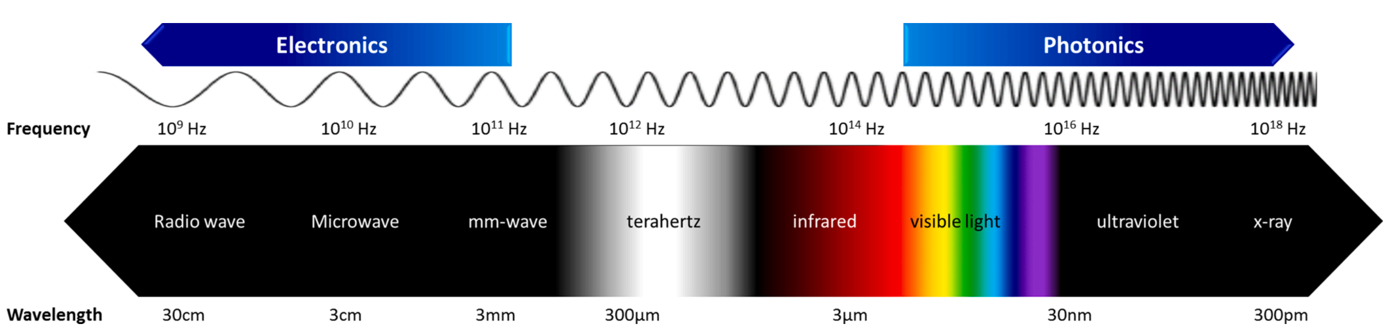

Fig. 1. THz band across electromagnetic spectrum.

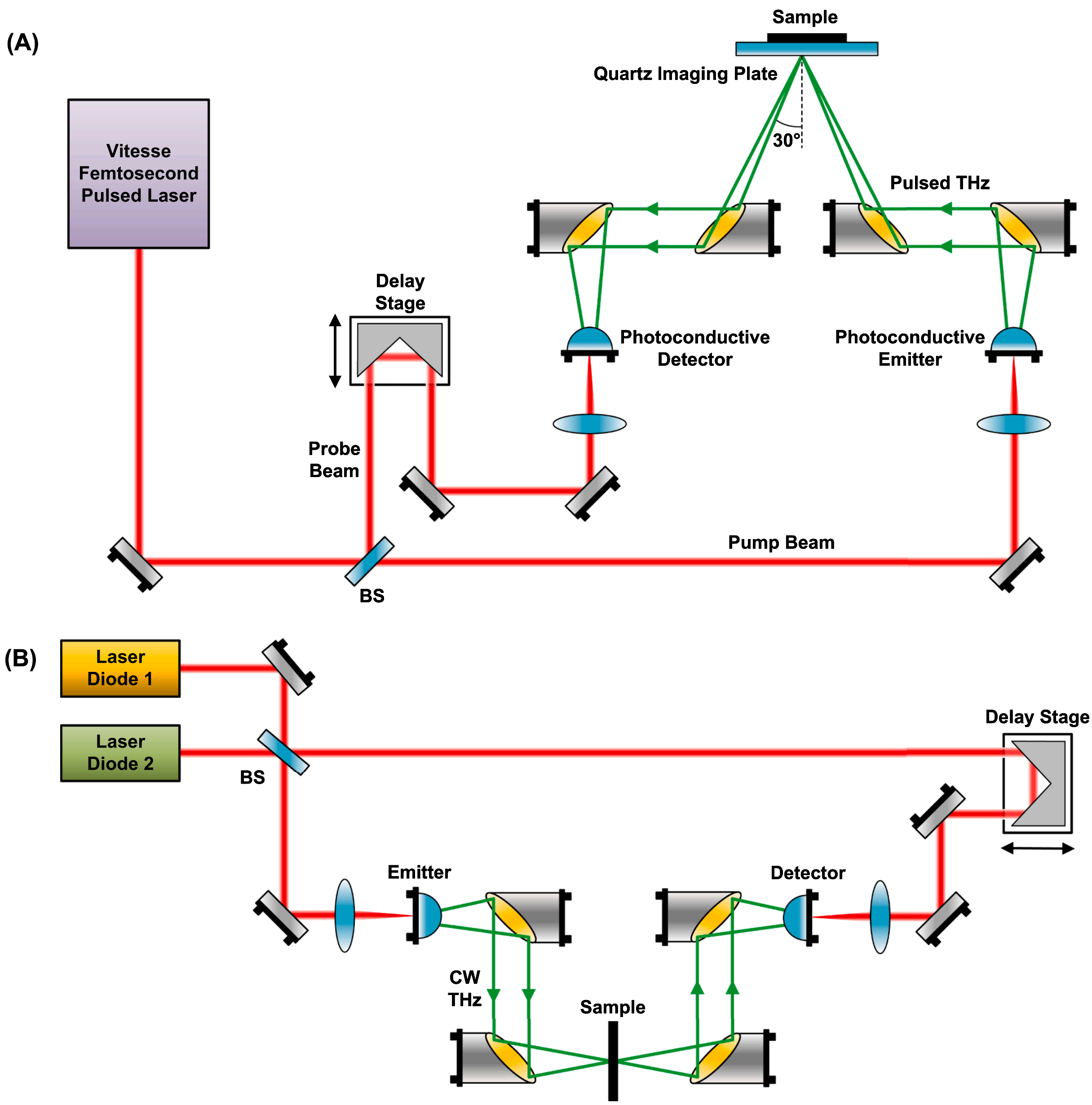

Fig. 2. Schematic illustration of THz imaging systems; (A) pulsed THz imaging using photoconductive antennas in a reflection-based geometry, (B) continuous-wave (CW) THz imaging using photomixers in a transmission-based geometry.

recommended to use non-ionizing diagnoses whenever they provide equivalent results to radiative diagnostic methods [28,29]. Hence, high-resolution imaging with minimal effect on biological tissue is another unmet demand in medical diagnostics.

The THz technique is non-ionizing radiation and compared to other traditional imaging techniques, THz waves carry very low energies in the femtojoule range that do not damage the specimen under study and makes it an attractive tool for non-destructive and non-invasive imaging, particularly for studying biological tissues [10,30,31].

Several researchers have studied the THz interactions with biological molecules, showing characteristic patterns in this specific EM region. THz technology renders an unparalleled medical diagnostic modality due to its high sensitivity to water content in the tissue [32]. Interaction of THz waves with the vibrational and rotational mode of water molecules enables a highly sensitive method to detect changes in water in biologic samples [33].

Broadband THz pulsed imaging has been employed to examine freshly excised healthy human tissue samples from skin, adipose tissue, striated muscle, vein, and nerve. The statistically significant difference in absorption coefficient was reported in the tissue samples based on the different degrees of hydration [34,35]. Compared to healthy tissue, increased vascularization is a hallmark of cancerous tissue, resulting in more significant amounts of interstitial water. Changes in water content can be mainly distinguished by mapping the elevated intensity of the THz reflection signal [36,37].

Sy et al. conducted another groundbreaking research to carry out the mechanism of THz cancer imaging. They realized that although THz absorption highly depends on changes in water content, formalin-fixed diseased samples enhanced THz properties, meaning water molecules should not be the sole source of distinction. They employed THz reflection spectroscopy to distinguish between normal and fixed formalin healthy and cirrhotic tissues. Both fresh and formalin-fixed cirrhotic liver tissue had a more prominent water content and absorption coefficient than the normal tissue. Evaluating histopathology results demonstrated that a higher absorption coefficient of diseased cirrhotic liver tissues than normal tissue was not only due to changes in water content but also indicated significant sensitivity to structural changes [38]. These results illustrate the feasibility of THz for *in-vivo* clinical study.

Ophthalmology

Due to the extreme sensitivity of THz absorption to tissue water content, this technique has been recently proposed as a noncontact scanning in ophthalmology [39]. Traditional imaging technologies such as current imaging tools, such as anterior segment optical coherence tomography (ASOCT) or ultrasound pachymetry scan human cornea tissue to measure the corneal thickness [40]. By contrast, THz reflectometry allows topographical monitoring of abnormality and sensing corneal hydration level as a biomarker to evaluate corneal edema and scar after eye injury, glaucoma filtrating, or cataract surgery [39,41,42].

Dental imaging

Dental caries is the most prevalent chronic disease worldwide, especially in children and youth. If they are not treated at this preliminary stage, demineralization will spread through the dentin, which leads to advanced cavities and dental losses. The annual expenditure on oral healthcare would be extraordinarily high compared to cancer. The early detection of dental caries is a pivotal demand in preventive and therapeutic dentistry to prevent invasive treatment and save healthcare costs. However, commonly used dental imaging modalities have poor sensitivity to detect and monitor the progression of carious lesions at early stages.

In contrast, other highly sensitive imaging relies on ionizing x-ray, which raises health concerns and cannot be employed for frequent imaging over a short period of time [23,43]. Recently, THz Pulsed Imaging (TPI) has been used to generate 2D and 3D images of tooth structure for early detection of dental diseases and imperfections without further concern. The path of the continuous THz wave was disturbed by the presence of dental caries, resulting in measurable scattering at the site of dental caries in the time-domain reflection mode [44].

Cancer diagnosis

Early detection of cancer followed by accurate tumor excision at the primary stages would be highly beneficial in translational clinical oncology to treat many patients at the early stages and reduce mortality. However, conventional diagnostic techniques such as palpation, photomicrograph, and x-ray imaging with poor spatial resolution, are unreliable for precisely determining the exact extent of the tumor.

THz imaging provides a promising non-invasive method in cancer diagnosis to precisely delineate the margins of the cancerous tissue. THz is of great interest, especially during surgery, and was used to image human breast tumors and protect normal adjacent tissue from further damage while minimizing the need for second surgical procedures [45]. This ability stem from monitoring change in the THz characteristic signals originating from intrinsic sensitivity of THz to variation of tissue structure, hydrogen bonds, and the level of interstitial water content caused by cancer [46,47].

In comparison to healthy tissues, cancerous tumors contain a higher amount of interstitial water. The extreme sensitivity of THz waves to the content of water molecules in the diseased tissue is the primary distinguishing mechanism in developing THz medical imaging for cancer diagnosis [35]. The higher water content, combined with structural changes such as increased cell, protein, and vascular density, renders a more significant THz absorption and refractive index for the tumoral tissue [37].

In addition, traditional medical imaging tools, including CT and MRI, have limitations in measuring surface tissues, namely skin tissue and digestive organs, mainly during surgical removal. However, THz offers an intraoperative mapping technology with unique resolution and penetration depth in acquiring images from the surface of biological tissues such as cancerous epithelial cells [48,49].

A THz probe has been utilized for real-time intra-operative imaging of removed tissue specimens during breast tumor resection surgery [50,51]. THz helped minimize further dissection and preserve healthy tissue. To take advantage of this non-invasive technology and facilitate delineation of carcinoma tumor margin prior to surgery, researchers from the UK developed a portable TPI to differentiate between basal cell carcinoma and normal tissue ex-vivo and *in-vivo* [52]. Reflected THz pulse manifested change between carcinoma cell and normal tissue. Structural and spectroscopic information obtained from TPI helped to more accurately distinguish the extent of lateral spreading and depth of carcinoma tumor in the terahertz image, which correlated well with histology results [52]. THz absorption of basal cell carcinoma was significantly higher than in healthy tissue, attributed to an increase in the interstitial water within the tumoral tissue or change in the vibrational modes of water molecules [53].

TPI also demonstrated high contrast resolution between healthy breast tissue and invasive ductal carcinoma due to the difference in the refractive index with a considerable specificity and sensitivity, which demonstrated the feasibility of using TPI to map the shape of breast tumor [45,54].

In another groundbreaking research, THz endoscopic imaging was proposed for colorectal cancer detection. Conventional colonoscopy, MRI, CT, PET, and optical endoscopy are the current standard imaging tools for colorectal cancer detection and removing the abnormal region. However, harmful X-rays irradiation of ionizing modalities such as MRI and CT these techniques cannot be employed in renal failure patients. Additionally, macroscopic tools such as optical endoscopy suffer from low-resolution images with less specificity. Biopsy samples may provide more valuable microscopic information.

Although the results of sampling and screening could be validated by histological analysis of biopsy samples, the procedure is highly dependent on the physician's visual inspection and experience, and there is no real-time imaging to validate biopsy excisions and accurate tumorous tissue delineation. Dorada et al. suggested integrated bendable endoscopic system with THz technology would upgrade *in-vivo* colorectal cancer imaging to detect and remove colon cancer tissue in real-time. THz endoscopy can discern between healthy and cancerous lesions since normal tissue is very homogenous at THz wavelengths while the tumorous and abnormal region has a dense structure containing larger colon nuclei with irregular shapes, which impair and increase refractive THz indices [13].

Furthermore, the capability of THz in monitoring molecular resonance in DNA provides a new opportunity to investigate biological macromolecule changes and DNA methylation as a carcinogenic fingerprint factor and define the incidence of cancer [55]. Observing the molecular resonance signal of genomic DNA using THz spectroscopy demonstrated that the spectral feature of the methylation signal of cancer DNA in the frequency range from 0.4 to 2.0 THz is a biomarker for the early detection of cancerous cells at the molecular level [55].

To date, an excisional biopsy is a gold standard for cancer diagnosis that removes the tumoral tissue to examine it under a microscope and detect signs of abnormality to define the type and stage of the disease. THz technology utilizes the sensitivity to the water content as the main biomarker and represents a vast potential to improve conventional biopsy by more precisely distinguishing tools. Additionally, THz could be employed intraoperatively in associated biopsy surgery to identify excised samples, thereby reducing the number of procedures and facilitating earlier and more accurate cancer diagnosis.

Even though THz imaging has yet to be ideally used for clinically early-stage cancer diagnosis, especially for deep-seated tumors, through the last decade, THz waves have been applied to distinguish cancerous cells in skin, liver, lung, breast, colorectal, and oral tissue [13,45,46,51,56–60]. Tremendous promising results proved that THz waves could be employed to ameliorate the accuracy of early cancer detection and confirmed the feasibility of this imaging technique for early detection and intraoperative clinical diagnosis of cancer [56].

On the contrary, the main noticeable challenge for THz imaging in living tissue is the limited contrast in a highly hydrated background. Although the difference in water content makes it possible for the THz to detect cancerous cells from normal tissue, a significant percentage of water in the living human body (up to 70%) may adversely influence on THz imaging and reduce *in-vivo* resolution [61].

To overcome this challenge and facilitate translational cancer diagnosis and clinical application of THz imaging, the contrast at the border of tumor and normal tissue should be intensified. Imaging contrast agents have been employed to enhance contrast in various medical imaging modalities such as MRI, CT and ultrasound.

Contrast agent nanoparticles robust THz medical imaging

As mentioned above, THz technology offers incomparable medical imaging that can detect changes in water content or tissue structure. However, widespread clinical application of conventional THz imaging is yet restricted since water molecules in the surrounding living tissue, strongly absorb THz pulses and significantly reduce imaging contrast [62].

In addition, limited target specificity and sensitivity of existing THz technology to accurately detect cancerous lesions hamper its clinical application. For instance, these deficiencies have made this technique impotent in distinguishing between malignant and benign tumors that confine THz imaging for translational oncology application [63]. Many efforts have been made to improve THz sensitivity and target specificity at cellular and molecular levels. One of these approaches is to develop and utilize nanoparticle probes as THz contrast agents to amplify the responding signal and improve imaging resolution [33,48,61,63].

During the last decade, nanotechnology offered promising potential to improve accuracy of THz medical imaging and facilitate clinical applications.Various nano-scaled materials such as multimodal imaging contrast agents have been investigated with various mechanism of action to manipulate impinging THz beam and escalate imaging sensitivity and specificity to enhance specific target for detailed cancer diagnosis at the early stages (Fig. 3) [63,64]. Following, we review nanoparticle contrast agents and their correspondence mechanism for THz cancer imaging.

Gold nanoparticles

Since THz absorption and reflection exhibited a sensitive correlation to the variation of water temperature, most of these nanoparticles benefit from the hyperthermia effect to enhance THz imaging contrast. Increasing water molecules' temperature modulates conformational motions and vibrational and hydrogen bonding, thereby significantly amplify the reflective index of the THz beam around the contrast agent [35,61,65].

Given this, metallic nanomaterial with photothermal behavior has been investigated as a contrast agent to intensify THz amplitude and enhance imaging contrast. The conventional THz time-domain reflection spectroscopy has been equipped with a near-infrared (NIR) laser system to trigger and monitor these nanoscale contrast agents. Irradiation of NIR beam induces surface plasmon polaritons (SPPs) on the surface of metallic nanoparticles. Localized surface plasmon resonance (LSPR) enhances light absorption and converts a significant portion of radiative energy into the heat that rises the local temperature, followed by enhancement of the THz signal in nearby water molecules [48,61,64,66].

Oh et al. designed photothermal Hz molecular imaging (TMI) by employing gold nanorods (GNRs) as a contrast agent to improve the sensitivity and target specificity of THz imaging for *in-vivo* cancer diagnosis. Their method can also monitor drug delivery processes at a high molecular level [48,64]. Various concentrations of GNRs were assessed to quantify detection sensitivity. *In-vitro* and *in-vivo* TMI showed remarkable linear correspondence between THz reflective signal

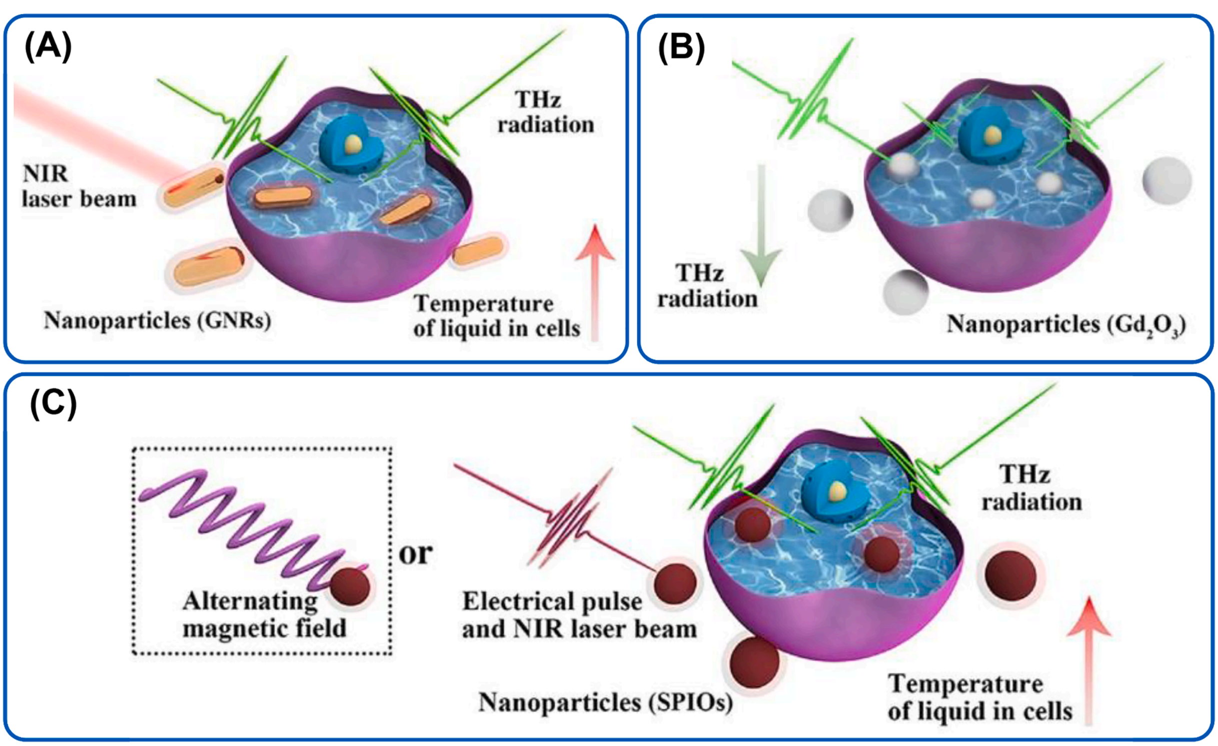

Fig. 3. (A) Schematic interaction of various nanoparticles to enhance THz imaging contrast: (A) excited GNR with NIR laser increase local temperature and modulate THz signal, (B) Responses of SPIO to the THz beam. (C) Illustration of Gd_2O_3 under alternating magnetic field or NIR irradiation modulate temperature of water followed by THz signal. Images reproduced with permission from [61].

and GNRs concentration. By reducing the concentration, subcutaneous injection of Matrigel containing 15 μM concentrations of gold nanoprobes into the mice exhibited the lowest detectable THz signal to discern tumor [48].

In addition, nanoparticle contrast agents can be functionalized to target specific cells to improve target specificity. GNRs were coated with polyethylene glycol and conjugated with Cetuximab for specific epidermal growth factor receptor (EGFR) tumor-cell targeting. Evaluating two kinds of epidermoid carcinoma cells with different levels of EGFR expression, A431 with overexpression of EGFR and MCF7 with lower expression of EGFR, proved that conjugated GNR nanoprobes considerably enhanced tumor target specificity and sensitivity of TMI to differentiate specific cancer biomarker at the cellular level (Fig. 3.c) [48].

Infrared illumination through the synergy of THz imaging and NIR laser-excited SPPs on the surface of GNRs elevated the temperature of local media around the nanorods and enhanced the reflective THz signal from the cancer cells by 20%, which resulted in rendering more accurate images at micron resolution [64].

Reflective THz signal highly depends on GNR concentration and NIR laser intensity (Fig. 4). Increasing IR laser intensity and GNRs concentration amplify THz reflection response from epidermoid carcinoma cells. However, only NIR illumination did not provoke the THz response in the absence of GNRs (Fig. 4.C) [64]. This shows contrast agents' exclusive pivotal role in inducing higher THz medical imaging contrast. Using differential mode, the THz signal from epidermoid carcinoma A431 cancer cells incubated with GNRs was 30 times higher than cancerous cells without GNRs (Fig. 4.E–J). Extreme enhanced sensitivity of THz imaging shows the feasibility of THz endoscopy that may facilitate the application of THz for early stages of clinical cancer diagnosis [64].

Considering gold as a promising contrast agent, various ongoing approaches such as alloying with Au with Palladium, Tantalum, or Iron have been proposed to enhance the efficiency of gold nanoprobes for THz cancer imaging [67].

Additionally, to design and employ contrast agents, especially for clinical THz imaging, developed nanoparticles should be biocompatible, without a significant degree of cytotoxicity or genotoxicity.

GNRs are typically synthesized by using cetyltrimethylammonium bromide as the most efficient stabilizing surfactant. However, for biological application, gold nanoparticles should be detoxified from cetyltrimethylammonium bromide due to its cytotoxicity and membrane-compromising concerns [68].

To reduce toxicity and ameliorate the long-term stability of the THz contrast agent, GNRs were coated with a silica layer which also maintained cellular uptake efficiency. Silica-coated gold nanoparticles represented improved biocompatibility and photothermal efficiency that led to higher contrast of THz reflective imaging compared to uncoated GNRs during *in-vitro* THz imaging of prostate cancer cells [69]. Analyzing cancerous prostate cells using silica-coated GNRs as a contrast-enhancing agent for THz imaging demonstrated a 25.35% higher intensity than the sample without nanoparticles [69]. It is worth mentioning that besides proper biocompatibility, the coating layer should also be transparent in the THz and IR spectrum, which makes silicon and Teflon® film favorable candidate for embedding gold nanoprobes for *in-vitro* THz imaging of malignant skin tumors in the transmission mode or *in-vivo* in reflection mode [67,70].

Magnetic iron oxide nanoparticles

Magnetic iron oxide nanoparticle is another metallic biomaterial that has been extensively studied in clinical oncology either as a diagnostic or therapeutic agent. Superparamagnetic iron oxide (SPIOs) nanoparticles served as a contrast agent for MRI imaging, targeting agent for gene and drug delivery, or magnetic hyperthermia for cancer treatment. Based on their successful application in MRI medical imaging and biomedicine, SPIO nanoparticles have been investigated as a multimodal contrast agent to enhance continuous THz wave imaging.

SPIOs can enhance THz signal intensity through dual-functioning magnetic and optical manipulation. Like GNRs, SPPs on the SPIOs surface can be triggered by NIR laser beams to modulate reflective THz waveforms. On the other hand, SPIOs can respond to the magnetic field and reduce the relaxation time of water protons [33,48].

Zhang et al. synthesized SPIO nanoparticles with an average diameter of about 8 nm and incorporated an alternating magnetic field into the THz device system to obtain magnetic induction heating of SPIOs. Induced heating from alternating magnetic field modulates reflected signal and can be further employed for real-time THz imaging. Due to a large amount of interstitial water in cancerous and normal tissues, they assessed water-based samples with different concentrations of SPIO to simulate *in-vivo* imaging from living tissue after endocytosis of SPIOs. They reported that solution containing SPIOs contrast agents enhanced highly sensitive reflection THz signal upon exposure to an alternating magnetic field. In the relative reflection change images, the average amplitude of solution with SPIOs was 29.41% ± 0.42%, which shows significant enhancement compared to 0.30% ± 0.03% for the water without SPIOs. Focal-plane imaging strategy was adopted to acquire real-time THz monitoring before and after exposure to the alternating magnetic field. Differential and relative reflection change focal-plane THz images illustrated dramatic contrast between water samples with and without 4 g/L SPIOs [71]. It is worth mentioning that SPIOs were able to enhance the contrast between cancerous and normal regions. Thereby SPIOs could be considered a reliable imaging contrast to distinguish between cancerous and normal tissues.

In another effort, commercially available SPIO contrast agents were utilized for THz imaging for human ovarian cancer diagnosis. Various concentrations of SPIOs; Feridex® were transfected into human ovarian cancer cells (SKOV3), and THz reflection imaging and MRI were employed to investigate magnetic and optical properties of SPIOs nanoparticles both *in-vivo* and *in-vitro*.

Both THz and T2 weighted MRI imaging from SPIOs-labeled SKOV3 tumors indicated similar dose-dependent patterns. THz images were whitened while T2 MRI images darkened along with increasing SPIOs concentration in samples. For *in-vivo* assessment, inoculated mice with SPIO-labeled SKOV3 cells were examined using MR and THz imaging over 1, 3, 7, and 14 days after inoculation. The signal intensity of both imaging modalities elevated with increasing SPIOs concentration and illustrated enhancement in the areas that contained SPIO-labeled SKOV3 cells.

Monitoring temporal THz waveforms of every single pixel in the THz images illustrated surface plasmon changes during irradiation with the Near-infrared (NIR) laser. The intensity of the THz image represented dramatic enhancement over the period of NIR irradiation, only in the pixels corresponding with SPIO-labeled SKOV3 cancer cells.

Another noticeable point is that signal intensity, and image contrast of both MRI and THz techniques gradually decreased over time; however the resolution of THz image adequately sustained dominance to clearly distinguish tumor margins (Fig. 5) [33].

Significant correlation between imaging data from excised or biopsied pathologic specimens with H&E and Prussian blue staining confirmed THz imaging as a reliable diagnostic modality like MRI. These results suggested that commercially available SPIOs;Feridex® may facilitate the application of highly sensitive target-specific TMI as one of the most promising tools for cellular and molecular studies with a clinical application in oncology diagnosis at an earlier stage [33].

Drug et al. developed a novel magnetite contrast agent for THz endoscopic imaging in gastroenterology. *In-vitro* assessment of functionalized either citric acid and carboxymethylcellulose as magnetite contrast nanoparticles on human gastric adenocarcinoma cell line represented a low impact on genetic material integrity of Gastric adenocarcinoma cell line and cell viability at low doses. The insignificant impact of these functionalized magnetite nanoparticles on cytotoxic and

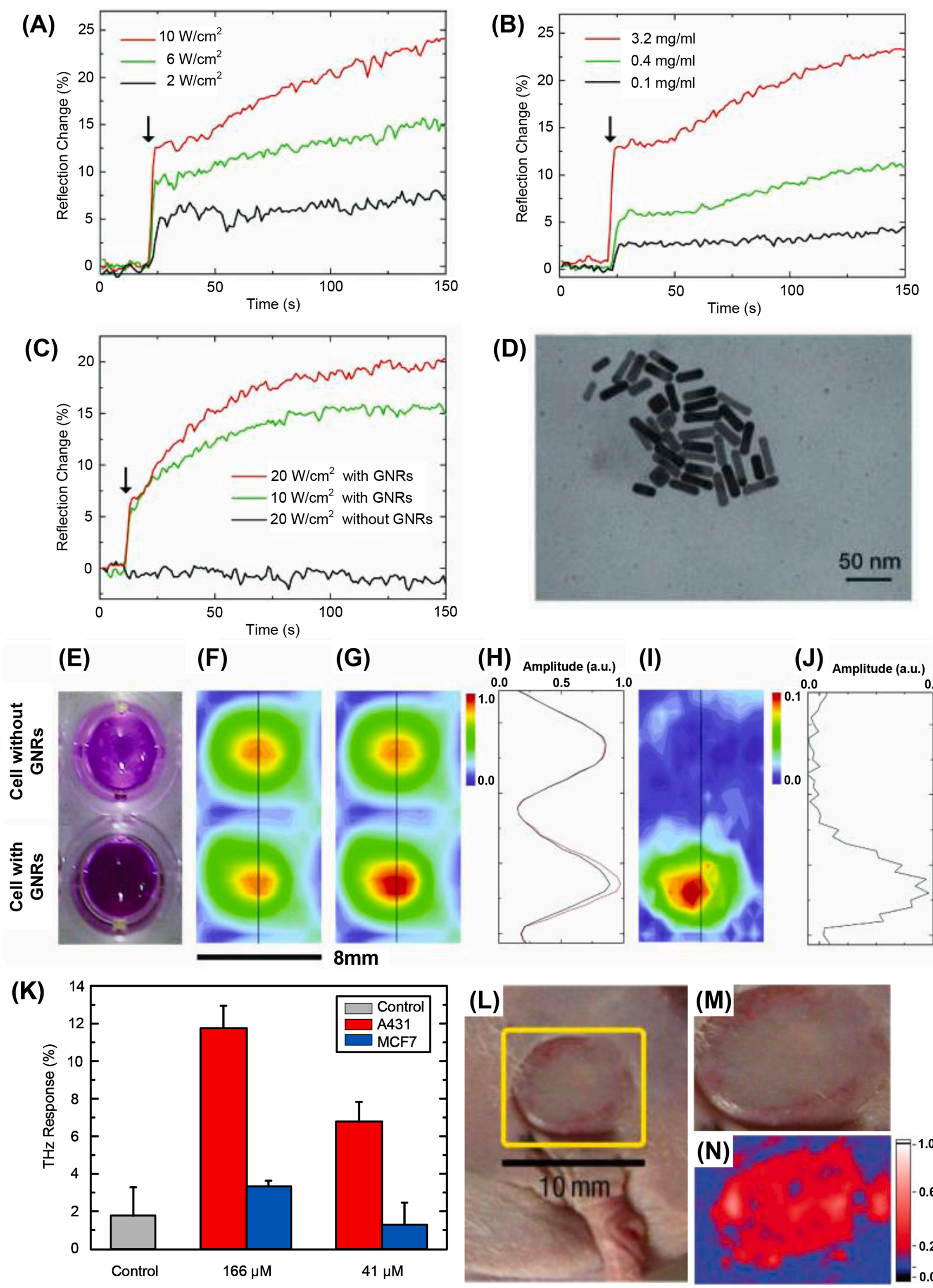

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Fig. 4. Seung Jae Oh et al. demonstrated that THz reflection signals depend on NIR laser intensity and can be enhanced with different concentration of GNR. Enhancement of THz response correlated with increasing (A) NIR laser beam intensity (B) GNR concenteration in the solution. (C) NIR laser irradiation trigger an abrupt increment in THz reflection amplitude only in the sample that contain GNRs. Although various laser intensity provokes different response, reflective response of sample without GNRs was regardless of NIR excitation and did not exhibit any changes, (D) TEM images of GNRs contrast agent investigated for THz imaging, E-(G) *In-vitro* images of epidermoid carcinoma A431 cell cultured with and without GNRs; (E) Visible image, F) THz image without NIR illumination, (G) THz image with NIR irradiation, H) Reflection amplitudes along the lines exhibit 10% enhancement red (G) compared to black graph (F), (I) differential image between (F) and (G) significantly demonstrated the effect of activated GNRs in improving contrast, (J) amplitude along the line in (I). (K) They also evaluated *in vitro* and *in vivo* effect of GNR on target specificity and sensitivity of THz molecular imaging. For this purpose, GNR were coated with polyethylene glycol (PEGylate) and conjugated with Cetuximab for epidermal growth factor receptor (EGFR) specific tumor-cell targeting. Grey bar is control sample that represent the THz response from the A431 cells without GNRs. The red and blue bars illustrate the A431 (EGFR over-expressed) and MCF7 (EGFR less expressed) cells, respectively, targeted with GNRs at different concentrations of 166 μM and 41 μM. This graph shows that GNRs can be conjugated to target specific cancerous cells and differentiate tissue with remarkable sensitivity at the cellular level. (L–N) To investigate *In vivo* and ex vivo capability of THz for cancer detection, THz molecular image of the mouse with an A431 tumor (N) compared with the correspondence optical images of the same tissue (L, M). Images reprinted with permission from [48,64] © The Optical Society.

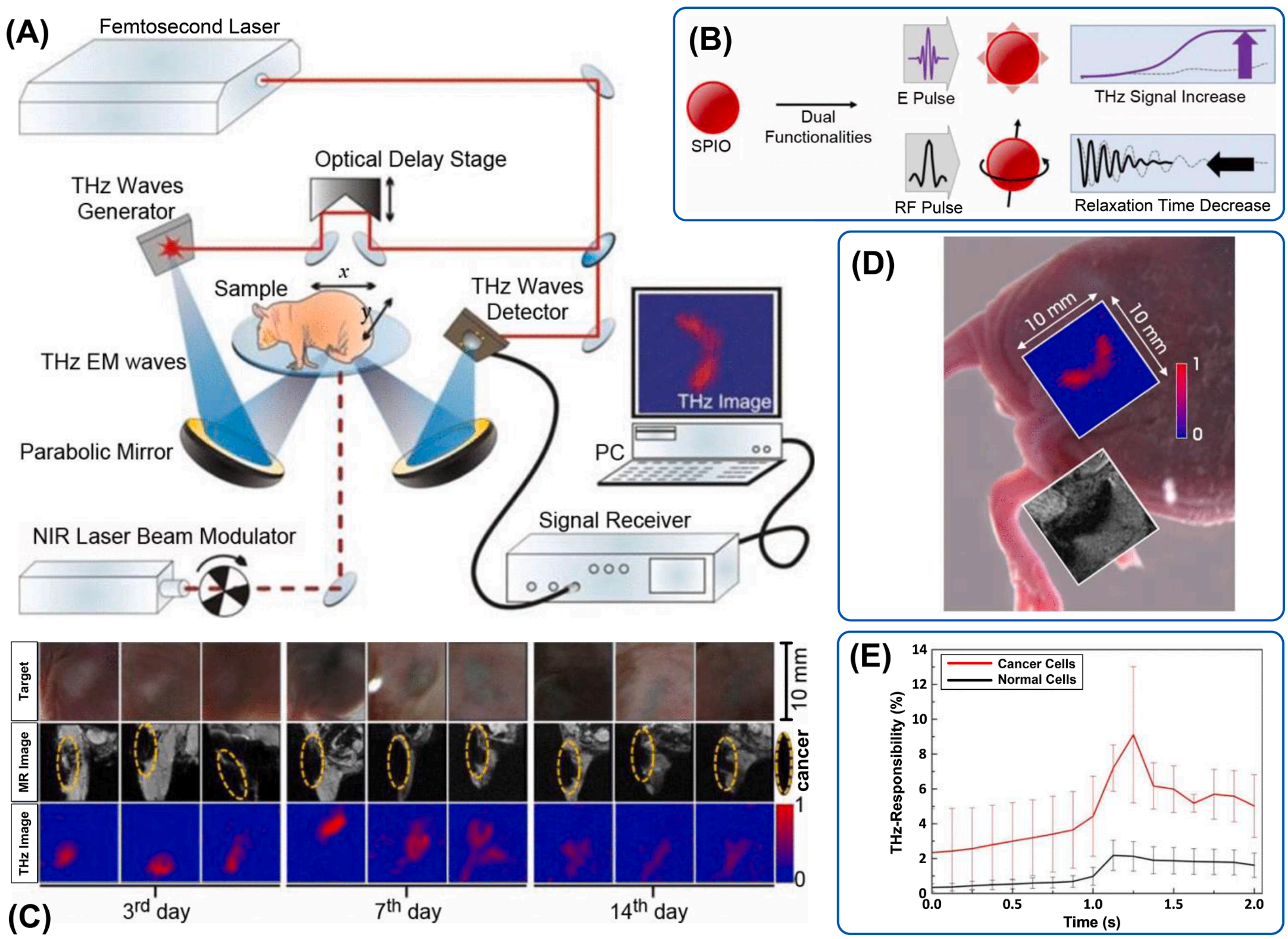

Fig. 5. (A) Integrated THz imaging set-up with a NIR laser illumination for the *in-vivo* imaging of ovarian cancer enable measurable contrast to deffine tumor margins, (B) Schematic illustration of the dual electrical and magnetic function of SPIO nanoparticles during THz and MRI. Magnetic behavior of SPIOs during MRI decrease relaxation time of water protons. However, in the course of the electric field of THz imaging SPP on the surface of SPIOs increases the THz signal amplitude, (C) Correspondence MRI and THz images of SKOV3 cells of mice shows the effect of SPIO contrast enhancement during 3,7, and 14 days, (D) *In-vivo* THz and MRI molecular images of the right thighs of mouse injected with SPIO-labeled ovarian cancer cells after 24 h, (E) 2 s time course of TMI signal with a peak after NIR laser illumination in 1s show significant difference between in THz response of cancer and normal cell. Images reproduced with permission from [33].

genotoxic suggested that they can be employed as safe contrast agents for THz endoscopic imaging in oncology diagnosis [72].

Gadolinium oxide nanoparticles

Gadolinium oxide (Gd_2O_3) nanoparticles (GONPs) are another multi-functional contrast enhancement that has been adapted from MRI contrast agents to enhance the sensitivity of THz medical imaging. However, GONPs have a different mechanism from the hyperthermia effect. GONPs received great attention for THz medical imaging since gadolinium can significantly absorb EM waves up to three times higher than water.

Lee et al. studied the feasibility of gadolinium-based nanoparticles as a contrast agent for THz cancer diagnosis. Samples with various GONPs concentrations were examined by THz time-domain spectroscopy and obtained results illustrated concentration-dependent optical constants of GONPs [73].

Increasing GONPs concentration results in the reduction of peak amplitude and delay in the phase of each sample. The waveform of each sample was compared with reference in the frequency domain to calculate the refractive index and the power absorption. Obtained results demonstrated that as the concentration of the GONPs increased, both refractive index and power absorption were elevated [73].

Considerable interaction between the THz waves and the GONPs provides an incredible accuracy in detecting Gd_2O_3 nanoparticles in a range of few PPMs and offers their application as multi-functional contrast agents for THz cancer imaging.

GONPs can be functionalized by an antigen or an antibody to target specific cancerous cells. Authors suggested that nanoparticles should be encapsulated in biocompatible materials to exploit GONPs for clinical human cancer diagnosis, improve THz imaging resolution, and prevent aggregation [73].

To enhance the specificity and resolution of MRI and THz imaging, Cristian et al. developed gadolinium oxide using coprecipitation to control nanoparticles size distribution more accurately and functionalized it as a biocompatible contrast agent in a range of 5 to 20 nm. Comparing MRI and THz ex-vivo images of biopsy samples of gastric/digestive cancer indicated that Gd_2O_3 had a more significant influence on THz image contrast than MRI imaging to distinguish between tumors and normal tissue. The finding suggested that GONPs supplement THz as safe and accurate imaging for early-stage cancer diagnosis [74].

Due to the significantly higher absorption of EM waves in comparison to gadolinium-based contrast agents would be a promising candidate for THz contrast agents to improve selectivity and contrast with the capability of surface modification to enhance target specificity [73,74].

Ongoing efforts are to design and develop novel contrast agents to amplify improve THz sensing efficiency and accurately distinguish cancerous tumor borders from healthy tissue. Multimodal nano contrast particles were discussed with capability to improve the THz images contrast and target specific cancerous biomarkers [33,35,61,65,72-75]. Given that this interdisciplinary approach can enhance the capability of THz imaging for clinical cancer diagnosis. Table 1 presents a list of the most investigated nanoparticles as THz contrast agents for cancer diagnosis.

Table 1
Contrast agent nanoparticles to robust THz medical imaging.

Material	target	Application	Ref.
Gold Nanorods	Carcinoma tumor	Enhance the sensitivity of photothermal THz imaging by plasmonic resonance on the surface of gold nanorods. These nanoprobes were functionalized and conjugated with biological agents (Cetuximab) to improve targeting of specific cancer cells	[48]
Gold Nanorods	Epidermoid carcinoma A431 cell	NIR illuminated gold nanorods increased THz reflection amplitude from the cancer cells by 20% which is significant sensitivity enhancement of THz imaging to provided micron resolution images for cancer diagnosis.	[64]
Gold Nanorods	Prostate cancer	silica-coated gold nanorods enhanced intensity of the prostate cancerous cells as a biocompatible contrast agent	[69]
Gold Nanoparticles	*In-vitro* and *in-vivo* skin cancer	Embedded gold nanoparticles in Teflon® film as a transparent matrix in both THz and IR wavelength for *in vitro* and in human skin cancer *in vivo* THz imaging	[67,70]
Superparamagnetic Iron Oxide Nanoparticles (SPIOs)	Ovarian cancer	FDA approved SPIOs; Feridex® for MRI was investigated as a dual contrast agent for THz imaging. *In-vitro* and *in-vivo* imaging in SKOV3 cancer cells and mice using SPIO-labeled nanoparticles represented a significant correlation between MRI and THz imaging which proved feasibility of THz imaging for early diagnosis of ovarian tumors	[33]
Superparamagnetic Iron Oxide Nanoparticles (SPIOs)		SPIOs developed as contrast-enhancement agent for continuous THz wave imaging based on magnetic induction heating. SPIOs contained samples under alternating magnetic field exposure demonstrated significant enhancement in THz signals	[71]
Magnetite Nanoparticles	Human Gastric adenocarcinoma cell line (AGS)	*in-vitro* assessment of magnetite functionalized either citric acid and carboxymethylcellulose nanoparticles as THz contrast agent for gastrointestinal endoscopy	[72]
Gadolinium Oxide (Gd_2O_3) Nanoplates		Evaluate improvement in sensitivity and constant of THz Imaging by using various concentration of Gadolinium Oxide Nanoparticles as Contrast Agents	[73]
Gadolinium Oxide (Gd_2O_3) Nanoplates	Gastric/digestive cancer; AGS	Development of nano-scale biocompatible Gadolinium Oxide for both MRI and THz medical imaging to improve the accuracy and resolution for early detection of cancer	[77]

Future perspective of THz medical imaging

Recently, extensive interdisciplinary research in electronic, photonic, semiconductor, material science, image processing, bioengineering, and nanotechnology has been carried out to expand THz technology and thrust this unparalleled non-invasive imaging tool into the limelight for biomedical application.

Specifically, in cancer diagnosis, THz imaging systems have been mostly proposed to help clinical oncologists for early detection of abnormality or intraoperatively assist them in precisely excising tumorous tissue and facilitating point-of-care testing.

Although THz biosensing has offered breakthroughs in biomedicine, it still has some challenges, including limited contrast to accurately distinguish tumor margins in the hydrated environment which hamper clinical monitoring application [56]. Highly sensitive THz imaging equipped with functionalized nanoparticles would be a reliable technique for early cancer detection.

Many studies have analyzed the biological effects of contrast nanoparticles and suggested that the size, shape, dose, surface charge, and hydrophobicity of nano agents may influence their toxicity, biocompatibility, and effectiveness [76–78].

Additionally, surface modification and stabilization are needed to prevent agglomeration during diagnostic and therapeutic [79].

Further research is required to develop novel nanoparticles and optimize synthesis protocol, surface modification, and administration routes to improve the specificity, sensitivity, distribution, and efficacy of contrast agents for THz medical imaging [80]. Labeling cancerous cells with contrast agent nanoparticles may facilitate the application of non-invasive THz imaging in cellular and molecular studies or clinical diagnosis to identify cancer *in-vitro* and *in-vivo* [33,56].

Conclusion

The application of THz technology to evaluate the biological pattern of biomolecules and living tissue is still in the early research phase. The non-ionizing and high sensitivity of THz wave to water content, hydrogen bonds, and tissue structure makes it favorable for clinical cancer diagnosis. Although there is an intense desire to employ THz imaging as a safe and non-invasive modality for more accurate early detection of cancer, a large amount of interstitial water in living tissue interpretation of images could be challenging. Thus, THz cannot be ideally used for clinical cancer diagnosis, especially for deep-seated tumors. Contrast agents may play a game-changing role in enhancing the sensitivity and specificity of THz imaging for preoperative and intraoperative assessment. Recent advances in developing THz technology and providing THz imaging with nanoparticle contrast agents may overcome limited *in-vivo* sensitivity and significantly enhance the image's contrast. These advancements empower THz imaging to be utilized as a novel reliable medical diagnostic tool for cancer diagnosis and translational oncology.

CRediT authorship contribution statement

Ali Sadeghi: Data curation, Writing – original draft, Writing – review & editing. **S. M. Hossein Naghavi:** Data curation, Writing – original draft, Writing – review & editing. **Masoud Mozafari:** Data curation, Writing – original draft, Writing – review & editing. **Ehsan Afshari:** Data curation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

There are no conflicts of interest to be declared by the authors.

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