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Recent advances in photothermal nanomaterials-mediated detection of circulating tumor cells

Ruizhuo Ouyang, †*[a] Chongrui Geng,†[a] Jun Li,†[b] Qiliang Jiang,†[c] Hongyu Shen,[a] Yulong Zhang,[a] Xueyu Liu,[a] Baolin Liu,[d] Jingxiang Wu[c] and Yuqing Miao [a]

Photothermal materials have shown great potential for cancer detection and treatment due to their excellent photothermal effects. Circulating tumor cells (CTCs) are tumor cells that are shed from the primary tumor into the blood and metastasize. In contrast to other tumor markers that are free in the blood, CTCs are a collective term for all types of tumor cells present in the peripheral blood, a source of tumor metastasis, and clear evidence of tumor presence. CTCs detection enables early detection, diagnosis and treatment of tumors, and plays an important role in cancer prevention and treatment. This review summarizes the application of various photothermal materials in CTC detection, including gold, carbon, molybdenum, phosphorus, *etc.* and describes the significance of CTC detection for early tumor diagnosis and tumor prognosis. Focus is also put on how various photothermal materials play their roles in CTCs detection, including CT, imaging and photoacoustic and therapeutic roles. The physicochemical properties, shapes, and photothermal properties of various photothermal materials are discussed to improve the detection sensitivity and efficiency and to reduce the damage to normal cells. These photothermal materials are capable of converting radiant light energy into thermal energy for highly-sensitive CTCs detection and improving their photothermal properties by various methods, and have achieved good results in various experiments. The use of photothermal materials for CTCs detection is becoming more and more widespread and can be of significant help in early cancer screening and later treatment.

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[a]*School of Materials and Chemistry & Institute of Bismuth Science, University of Shanghai for Science and Technology, Shanghai 200093, China. E-mail: ouyangrz@usst.edu.cn*

[b]*Hunan Shizhuyuan Nonferrous Metals Co., Ltd, Chenzhou, Hunan 423037, China*

[c]*Shanghai Chest Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai 200030, China*

[d]*School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai 200093, China*

† R. Ouyang, C. Geng, J. Li and Q. Jiang contributed equally to this work.

Ruizhuo Ouyang

Ruizhuo Ouyang is currently the Hujiang Professor and Dean of the Department of Chemistry, School of Materials and Chemistry, University of Shanghai for Science and Technology. Her research mainly focuses on the design and preparation of various metal-based nanomaterials, especially bismuth and rhenium-based nanomaterials for their applications in biomedicine and biomedical analysis. She has published over 100 research papers, with two ESI highly cited papers included.

Chongrui Geng

Chongrui Geng received his B.E. degree from Shandong University of Technology, and is currently working toward an MS in chemical engineering within Dr Ruizhuo Ouyang's group. His research focuses on the application of photothermal nanomaterials in the detection of cycle tumor cells (CTCs).

1. Introduction

Most cancer deaths are caused by metastasis of tumor cells.[1] Researchers have invested enormous human, material and financial resources into exploring new ways to beat cancer. However, the complexity, diversity and specificity of cancer pose a huge obstacle to the development of cancer diagnosis and treatment.[2] With the advancement of science and technology, innovative methods for early detection and treatment of early-stage cancer have been discovered during the research conducted by scientists. With the rapid development of medical imaging technologies, such as fluorescence imaging, magnetic resonance imaging (MRI), ultrasound (US) imaging, photoacoustic (PA) imaging, computed tomography (CT) imaging, positron emission tomography (PET) imaging, and single photon emission computed tomography (SPECT) imaging. Early diagnosis and personalized treatment of tumors have become an effective way to control the rising mortality rate.[3]

However, the level of cancer cells in early body fluids is extremely low and difficult to detect by conventional methods. So far, a variety of cancer cell detection methods based on different technologies have been reported, such as electrochemical,[4] fluorescence,[5] magnetic,[6] Raman spectroscopy,[7] microfluidic[8] and colorimetric[9] methods. Although these detection methods can achieve accurate and highly sensitive detection of cancer cells, they are costly, complicated to operate, and even require large dedicated instruments, which can only be used in specific environments with low efficiency.

Circulating tumor cells (CTCs) are derived from tumor cells in the peripheral blood. Solid tumors release a surprising number of circulating tumor cells into the circulation of the blood, which under certain conditions separate from the primary or secondary

Qiliang Jiang

Qiliang Jiang received his MD degree from Shanghai Jiao Tong University, School of Medicine, Shanghai, China. He worked as a research fellow for 2 years in Hamamatsu University School of Medicine, Hamamatsu, Japan and Cleveland Clinic, Cleveland, USA doing research training. Currently he is an associate chief physician in the department of anesthesiology of Shanghai Chest Hospital. His research mainly focuses on myocardial protection and lung protection.

Jingxiang Wu

Professor Jingxiang Wu is the Director of the Department of Anesthesiology at the Shanghai Chest Hospital, affiliated to Shanghai Jiao Tong University. He also serves as the Vice Chair of the Thoracic Anesthesia Branch within the Chinese Society of Cardiothoracic and Vascular Anesthesiology. His research interests include anesthesia and pain management for cardiothoracic surgery, the mechanisms of pain associated with cancer bone metastasis, and the development of photothermal nanoparticles for the treatment of bone metastatic pain. He has published over 60 high-impact papers and been awarded the silver award at the 34th Shanghai Outstanding Invention Selection Competition and the third prize in the Shanghai Medical Science and Technology Awards.

Baolin Liu

Professor Baolin Liu is a Research Professor at the University of Shanghai for Science and Technology. His research focuses on the cryopreservation of human cells, tissues, and organs. He has served on several high-level boards and committees including the Biomedical Engineering Discipline of Shanghai, and the Society for Refrigeration of Shanghai, China. He was an executive director of the Society for Biomedical Engineering of Shanghai, a committee member of the Committee of Cryobiology, and the Society for Refrigeration of China.

Yuqing Miao

Professor Yuqing Miao is a fellow of the Royal Society of Chemistry, and a member of the editorial board of Chinese Chemical Letters and Frontiers in Chemistry. His main research interests are focused on electrocatalysis or photocatalysis of nanomaterials, especially bismuth and rhenium-based nanomaterials, and their applications in biomedicine, energy, environment, and biomedical analysis. He has published over 200 research papers, with two ESI highly cited papers included.

tumor of the cancer patient into the circulation of the blood and undergo metastasis. During metastasis, cancer cells undergo changes in cellular state, thereby acquiring characteristics necessary for cell survival, proliferation, and growth.[10] Most of these cells will apoptose in the circulation, and only a small fraction will survive and enter organs to cause organ lesions.[11] CTCs are very rare in the blood, and may contain only a few to a few dozen CTCs per 10 ml of blood, at a frequency of about one part in a few hundred million blood cells. This makes the isolation and identification of such circulating tumor cells a major technical challenge.[12] Numerous studies have shown that CTCs are present in the blood in free or clumped form and that tumor cells undergo epithelial–mesenchymal transition (EMT) during their entry into the circulation, thereby increasing their metastatic potential.[13] Tumor mutations and phenotypes are dynamic and require constant monitoring of cancer patients to provide up-to-date and effective care. The detection of CTCs can provide information on tumor DNA, RNA, and proteins that can help in the diagnosis, prognosis, and treatment of patients.[14] In addition, the number of CTCs detected can be helpful for the treatment and prognostic value of tumors.[15] CTC counting and molecular analysis may provide new means to detect cancer in real time and make individualized treatment decisions.[16]

Photothermal detection, a new method, uses the excellent photothermal properties of materials to convert light energy into heat energy under near-infrared light irradiation for the purpose of detecting cancer cells or other biomolecules by monitoring temperature changes.[17]

This review focuses on the background of the application and metastatic mechanism of CTCs and describes the significance of CTCs detection for early tumor diagnosis and tumor prognosis. It also focuses on how various photothermal materials play their roles in CTCs detection, including CT, imaging and photoacoustic and therapeutic roles. The physicochemical properties, shapes, and photothermal properties of various photothermal materials are discussed to improve the detection sensitivity and efficiency and to reduce the damage to normal cells. These photothermal materials are able to detect more accurately the microscopic number of CTCs in the blood through their excellent photothermal effects.

2. CTCs assay

2.1 Liquid biopsy

Liquid biopsy is a rapid and easy method for detecting cancer information in blood, mainly for detecting circulating tumor DNA (ctDNA) and CTCs in blood, and can be used for a variety of clinical applications.[18] Since solid biopsy requires tissue extraction from the patient, which is more dangerous for the patient, and tissue biopsy has many limitations to capture the genetic heterogeneity of cells within the tumor and metastatic cells.[19] Liquid biopsy mainly analyzes the patient's blood for biomarkers, which does not require surgery and is not harmful to the patient's body. The analysis of biomarkers such as CTC and ctDNA can provide a better understanding of the changes in cancer during the treatment process.[20] ctDNA and CTCs in blood have strong applications for cancer screening and diagnosis in the future as a companion diagnosis for molecularly targeted cancer therapy.[21] However, tumor heterogeneity is a significant barrier to treatment options for different

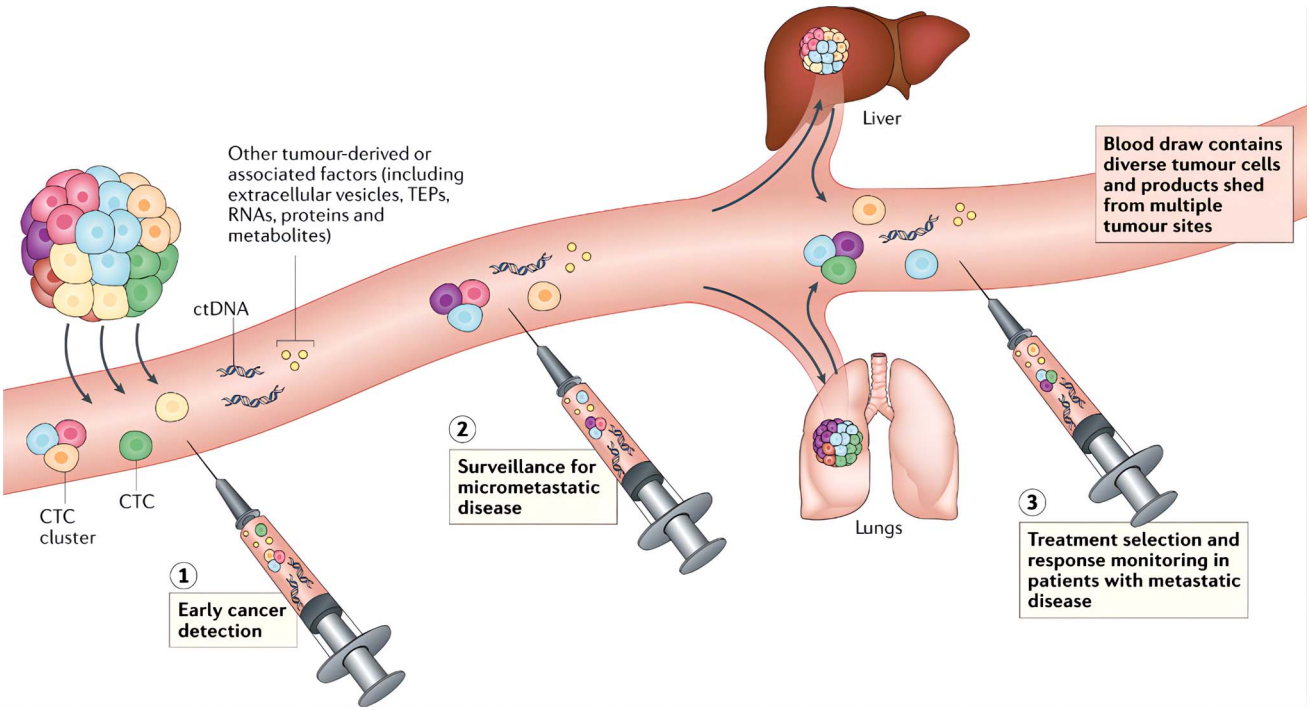

Fig. 1 Various clinical applications of liquid biopsy of CTCs, ctDNA or other derivatives in blood.[21] This figure has been adapted/reproduced from ref. 21 with permission from Springer Nature, copyright 2021.

individuals, ctDNA and CTCs play a key role in liquid biopsy diagnosis, which can be an effective alternative in cases where the primary tumor is difficult to biopsy[22] (Fig. 1). Thus, it is possible to extract molecular information about the parent tumor from these biomarkers and prescribe the right medicine.[23]

2.2 CTCs and CTC clusters

Cancer metastasis is a complex process that involves the infiltration, circulation, survival and attachment of cancer cells. CTCs are shed from the primary solid tumor and circulate into the bloodstream. Unlike other tumor cells, circulating tumor cells with epithelial–mesenchymal transition (EMT) readily shed or form clusters from the primary tumor and infiltrate into the bloodstream to metastasize (Fig. 2).[24] Since CTCs contain cellular analytes such as DNA, RNA and proteins of tumor cells, they have a natural advantage as biomarkers, and important information on tumor metastasis can be obtained by analyzing CTCs.[25] The ability of circulating tumor cells to form clusters is associated with their increased metastatic capacity.[26] Compared with individual CTCs, CTC clusters have a higher survival rate and penetrate faster and more efficiently than individual CTCs.[27] And CTC clusters are able to mediate metastasis with up to 100-fold better efficiency than single CTCs.[28]

2.3 CTCs detection technology

Detection of CTC is important for the diagnosis, treatment and early metastasis detection of tumors.[29] CTC detection technology should meet the following requirements: (1) high sensitivity and high capture,[30] (2) high specificity,[31] (3) high accuracy. (4) Low contamination,[32] (5) high recovery and high collection purity,[33] (6) ability to process a large number of samples in a short period of time. CTCs as a biomarker provides a highly effective and minimally invasive method for cancer diagnosis and prediction, which can replace some existing methods such as imaging techniques and solid tissue biopsy, and has an extremely high potential prognostic value in cancer diagnosis and treatment.[34]

Although CTCs have been discovered more than 100 years ago, so far only limited information has been available on the number and heterogeneity of these circulating tumor cells in

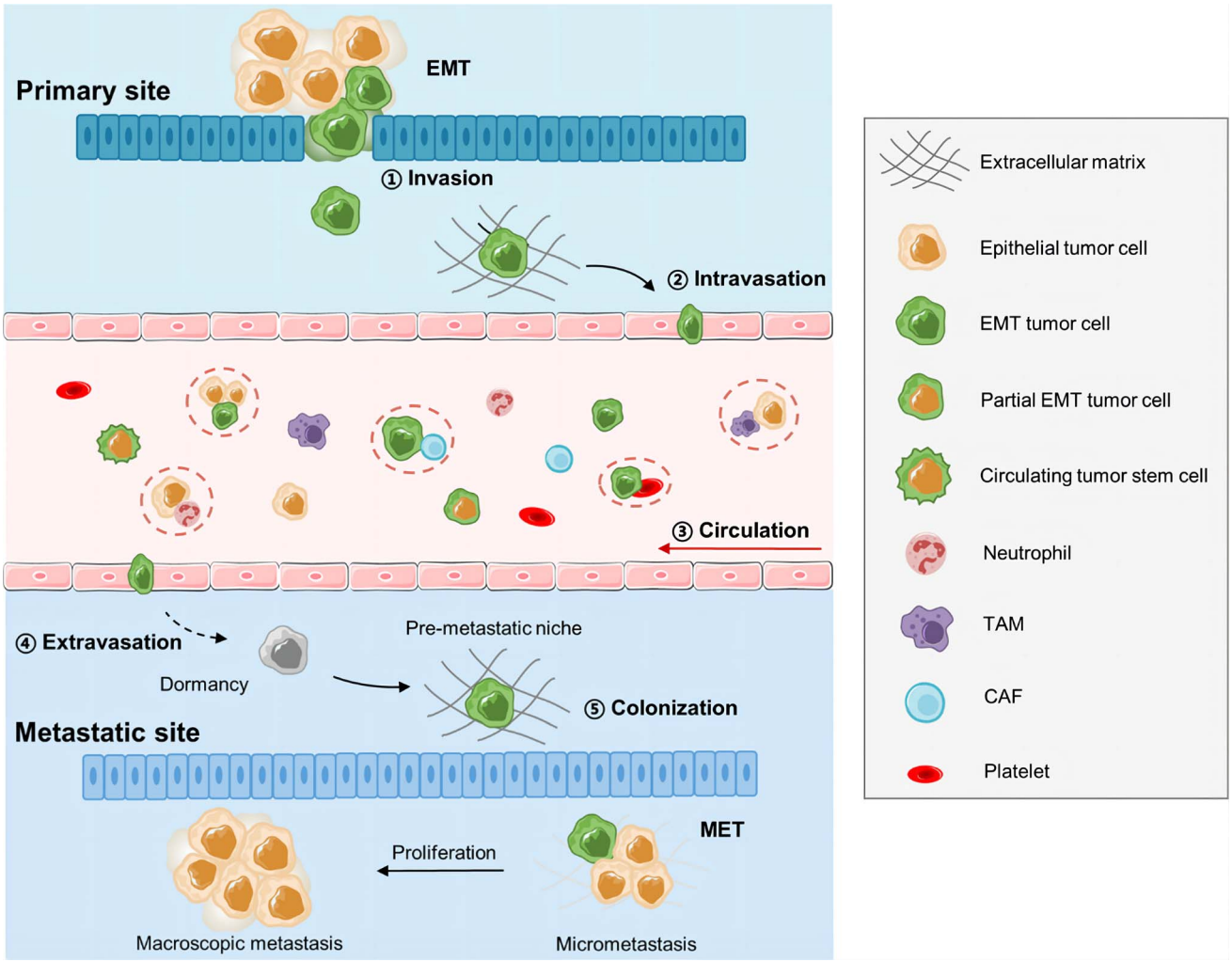

Fig. 2 Multi-step process of tumor metastasis. EMT: epithelial–mesenchymal transition, CAF: cancer-associated fibroblasts, TAM: tumor-associated macrophages.[24] This figure has been adapted/reproduced from ref. 24 with permission from Springer Nature, copyright 2021.

the blood at different stages and types of cancer, and their heterogeneity greatly affects cancer metastasis and malignancy.[35] nCTC detection, problems such as low accuracy and sensitivity are faced, and accurate and complete isolation of CTCs is very challenging.[12] The isolation and detection of circulating tumor cells are very important because they play a key role in the diagnosis and treatment of cancer.

Many methods have been developed to detect CTCs, including microfluidics, fluorescence, flow cytometry and electrochemistry. In recent years, microfluidics has been rapidly developed and has a wide range of applications in the medical field. Microfluidics can provide both analytical efficiency and high throughput capability without loss of precision. Microfluidic devices are small in size and miniaturized to save space and materials.[36] The combination of microfluidics and biosensing technology has further potential applications in circulating tumor cell enrichment. Compared with other CTCs enrichment methods, the currently popular microfluidics-based assays are less costly.[37] The combination of nanomaterials and microfluidic chips enables more sensitive detection of CTCs. Fluorescence is a promising tool for CTCs detection, and collection of cells from blood samples is essential epithelial antigens overexpressed on CTCs are detectable targets. Antigen-specific antibodies bind to nanomaterials and are an important marker in CTCs detection. However, EMT in CTC down-regulates epithelial phenotypes, such as EpCAM, making accurate CTCs detection challenging. Other commonly used detection and isolation methods include the CellSearch system,[38] immunocytochemistry (ICC),[39] and membrane filtration methods.[40]

Because CTCs are highly heterogeneous, they can lead to apoptosis even with relatively mild techniques.[41] Therefore, there is a need to find a new method that can rapidly and sensitively detect CTCs in the blood without destroying the cells. Current conventional identification methods not only affect the viability of cells, but also fail to identify the type of cancer cells when the disease is unknown. Therefore, new methods for identifying CTCs are urgently needed.[42]

3. Photothermal materials applied to CTCs detection

3.1 Photothermal effect of nanoparticles

With the advances in nanotechnology over the past 20 years, a range of highly promising nanotechnology-based assays have emerged for the detection and separation of CTCs in blood. The application of nanomaterials in biomedicine is an emerging field, and there has been a significant growth in the use of nanomaterials in cancer therapy due to their unique composition and properties.[43] The photothermal effect is the electrical change of a material due to temperature change when the material is irradiated by light. Near-infrared light (NIR) is a kind of ray that activates nanomaterials, and photothermal treatment of tumors is performed by irradiating nanomaterials with incoming infrared light.[44] Since the photothermal therapy (PPT) for cancer can be triggered locally to achieve therapeutic effects has received worldwide attention, through the unremitting efforts of researchers, nanomaterials that can convert radiant light energy into heat energy are gradually used in clinical practice to achieve therapeutic effects by interacting with NIR irradiation.[45] Currently, research on photothermal nanomaterials is mostly focused on cancer photothermal therapy, biomedical imaging, *etc.*, with relatively few reports on their use for CTC detection. For example, gold nanomaterials have been attracting much attention in the field of cancer photothermal therapy and imaging due to their shape and size variability[46] and good photothermal properties.[47] Synthesis of polyethylene glycol (PEG)-stabilized hybridized ultrasmall gold–silver nanotriangles and their application in photothermal therapy, proposed by Maturi *et al.* Dai *et al.* utilized gold nanorods and mesoporous silica for photothermal ablation and immuno-

Table 1 Analysis of photothermal materials applied to CTCs detection[a]

Materials	Cells	Features	Capture efficiency	Ref.
Au NFs	MCF-7	Enhanced surface-enhanced Raman scattering (SERS) and fluorescence	>90%	49
Au@CDs	MCF-7	High luminous efficiency		50
Large gold nanorods	RPMI-8226	Dynamic detection		51
Nanotube-CTC-chip	CK8/18, Her2, EGFR	CTCs preferentially adheres to the nanotube surface	>89%	52
Fe_3O_4@SiO_2/Tetra-DNA-Ag_2S	MCF-7	High detection sensitivity, strong resistance to background interference	97.63%	53
Silica nanowires	PC-3	Low cost and high efficiency	85.4 ± 8.3%	54
IMNs	MCF-7	Highly selective and accurate quantification	>80%	9
Cu_2O	MCF-7	Highly efficient magnetic capture and signal amplification	95%	55
BPNSs	HepG2	Catheter surface modified with anti-EpCAM antibody	5 min 2.1%	56
Gold nanoparticle (AuNP)–anchored BP nanosheets	MCF-7	High stability		57
MNPs-TA	MCF-7	Inhibits non-specific adhesion of mononuclear cells	95.1%	58

[a] MCF-7: human breast cancer cells; RPMI-8226: human multiple myeloma cells; CK8/18: cytokeratin 8/18; Her2: human epidermal growth factor receptor-2; EGFR: epidermal growth factor receptor; PC-3: human prostate cancer cells; HepG2: human hepatoma cells; IMNs: immunomagnetic nanoparticles; BPNS: black phosphorus nanosheets; MNPs: functionalized magnetic nanoparticles, TA: tannic acid.

blocking. These nanosystems have demonstrated good photothermal properties in biomedical applications, and the utilization of their photothermal properties can be extended to the field of CTC detection.[48] Therefore, the photothermal conversion efficiency of nanomaterials plays a crucial role in the detection of CTCs, as shown in Table 1.

3.2 Gold-based nanomaterials

Gold is one of the least reactive chemical elements. Gold is considered as a multifunctional material due to its antibacterial, anti-corrosion and chemical stability.[46] Gold-based nanomaterials are currently the most widely used nanomaterials. Because of their good photothermal and catalytic properties, gold nanomaterials are widely used in materials science, biomedicine, physics, chemistry, catalysis and electrochemical sensors.[59] The optical properties of gold and other inorganic nanomaterials are different, and gold exhibits strong absorbance under near-infrared light irradiation.[60] Gold nanoparticles are widely used in biomedical applications. The application of gold nanoparticles in medical direction depends on the physicochemical reaction between molecules and gold nanoparticles so that the surface properties of gold nanoparticles can be adjusted,[61] and different shapes of gold nanoparticles have different characteristics. Gold nanoparticles have good biocompatibility and controlled dispersion patterns, which make them significantly advantageous for cancer detection and treatment.[62] Gold nanoparticles have the ability to covalently or non-covalently interact with other materials through surface modification, which is well suited for drug delivery and targeted therapeutic purposes (Fig. 4).[63] The binding between gold nanoparticles and CTCs can be monitored quantitatively by photoacoustic signals or surface plasmon resonance

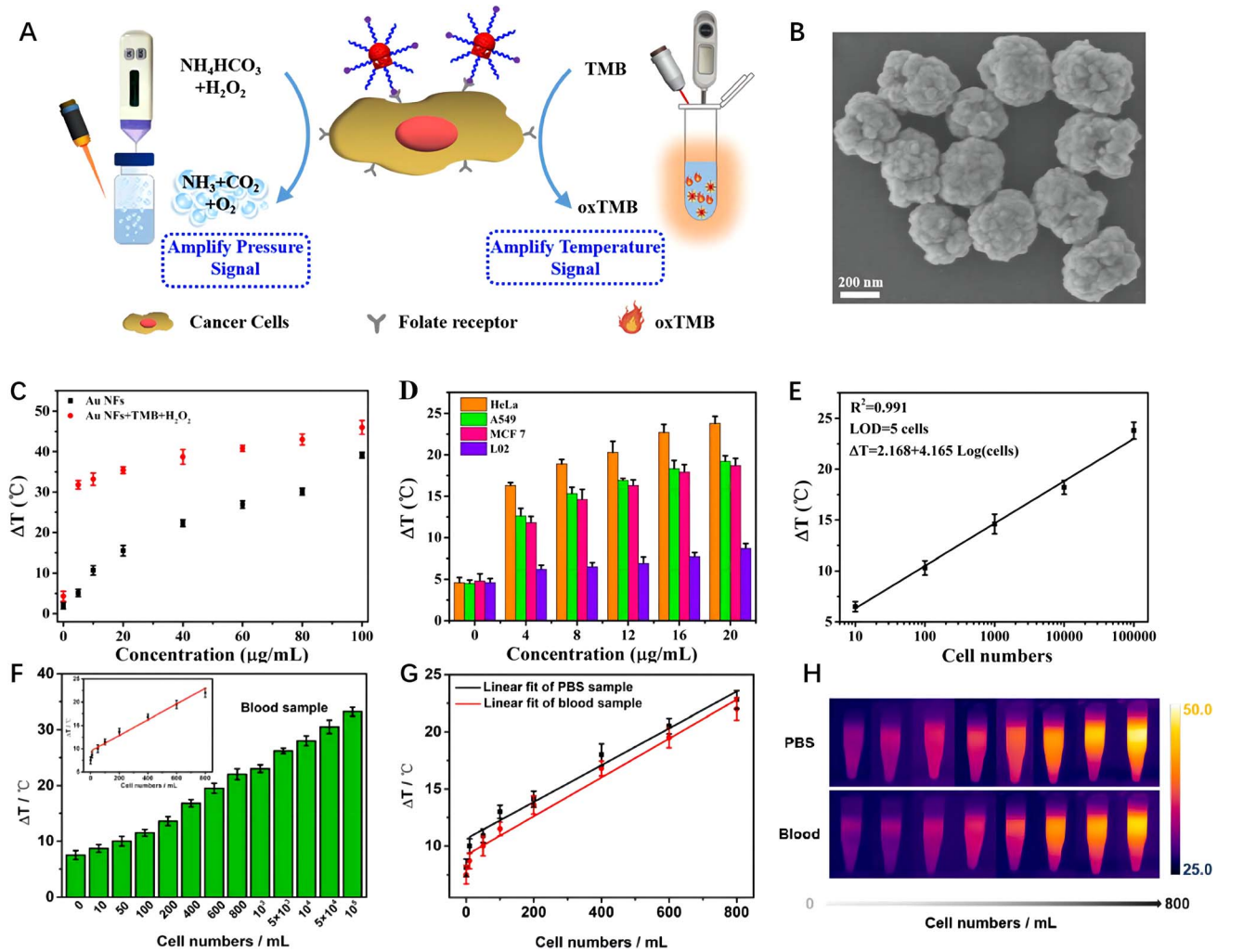

Fig. 3 (A) Schematic diagram of pressure-based and temperature-based detection platform. (B) Au NFs. (C) ΔT of Au NFs and the Au NF-mediated TMB–H_2O_2 system at different concentrations of Au NFs under irradiation of an 808 nm laser. (D) ΔT curves of cells incubated with FA-Au NFs in PBS samples, and (E) linear relationship between ΔT and log(number of cells) in PBS samples.[67] (F) Temperature change of FA-PtCPs NRs-mediated TMB photothermal effect detection system as a function of HeLa cell concentration in samples under 660 nm laser irradiation. (G) Quantitative curves and (H) IR thermal images of cancer cell temperature detection in PBS and whole blood samples. Error lines are indicated as mean ± SD.[68] This figure has been adapted/reproduced from ref. 67 and 68 with permission from American Chemical Society and Elsevier, copyright 2021.

(SPR) shifts.[64] And due to their unique properties and high versatility, they can play a great role in cancer early detection to diagnosis and treatment.[65]

Liu *et al.* synthesized Au@CDs by heating aqueous solutions of carbon dots (CDs) and HAuCl4 to boiling, and further used Au@CDs to develop a sensitive cell sensor that can directly detect CTCs in serum by attaching cell-specific aptamers.[50]

The visualization and quantitative analysis of CTC is achieved by recording temperature signal changes with a simple thermometer. Compared with traditional gene detection methods, it eliminates the need for labeling and amplification, and enables convenient and rapid detection of CTC without the aid of any advanced analytical instruments.[17,66] Liu *et al.* synthesized folate-Au nanoframeworks (FA-Au NFs) with dual detection of CTCs by pressure and temperature signals for highly sensitive and accurate detection of CTCs by portable manometers and thermometers circulating tumor cells with excellent peroxidase activity and excellent photothermal properties can promote the decomposition of NH_4HCO_3 and H_2O_2 to generate the corresponding gases (CO_2, NH_3 and O_2), thus amplifying the pressure signal in the closed reaction vessel. Moreover, Au NFs can catalyze the oxidation of 3,3′,5,5′-tetramethylbenzidine (TMB) to TMB oxide (oxTMB) with strong photothermal effect, thus amplifying the photothermal signal synergistically with Au NFs.[67] Li *et al.* passed folic acid (FA)-conjugated platinum(IV) methylene blue (MB) coordination polymer nanorods (FA-PtCPs NRs) (Fig. 3). This detection platform, irradiated by a 660 nm laser, converts the molecular recognition signal between FA and the folate receptor of cancer cells into a readable temperature value directly readable by a common thermometer with a detection limit as low as 2 cells per ml. This photothermal sensing platform provides a prospective strategy for the detection of circulating tumor cells and is expected to be widely used in future medical systems.[68]

3.2.1 Gold nanorods (GNRs). GNRs are a kind of rod-shaped nanoparticles that have been more widely used in recent years due to their anisotropic shape and tunable plasma properties. With the continuous improvement of synthesis methods, various materials are combined with or attached to gold nanoparticles to enhance and so on their ionophore properties.[69] GNRs have a significant role in the direction of bioimaging, photothermal therapy, and drug delivery,[70] have a remarkable ability to convert light into heat, have a strong absorption band under NIR irradiation, and exhibit good photothermal effects.[71] The high extinction coefficient of gold nanorods is an important indicator of their absorbed energy, depending on the laser power, radiation time, *etc.* to make their temperature changes occur. GNRs, like other gold nanoparticles, absorb light under near-infrared light irradiation to generate heat to increase the local temperature.

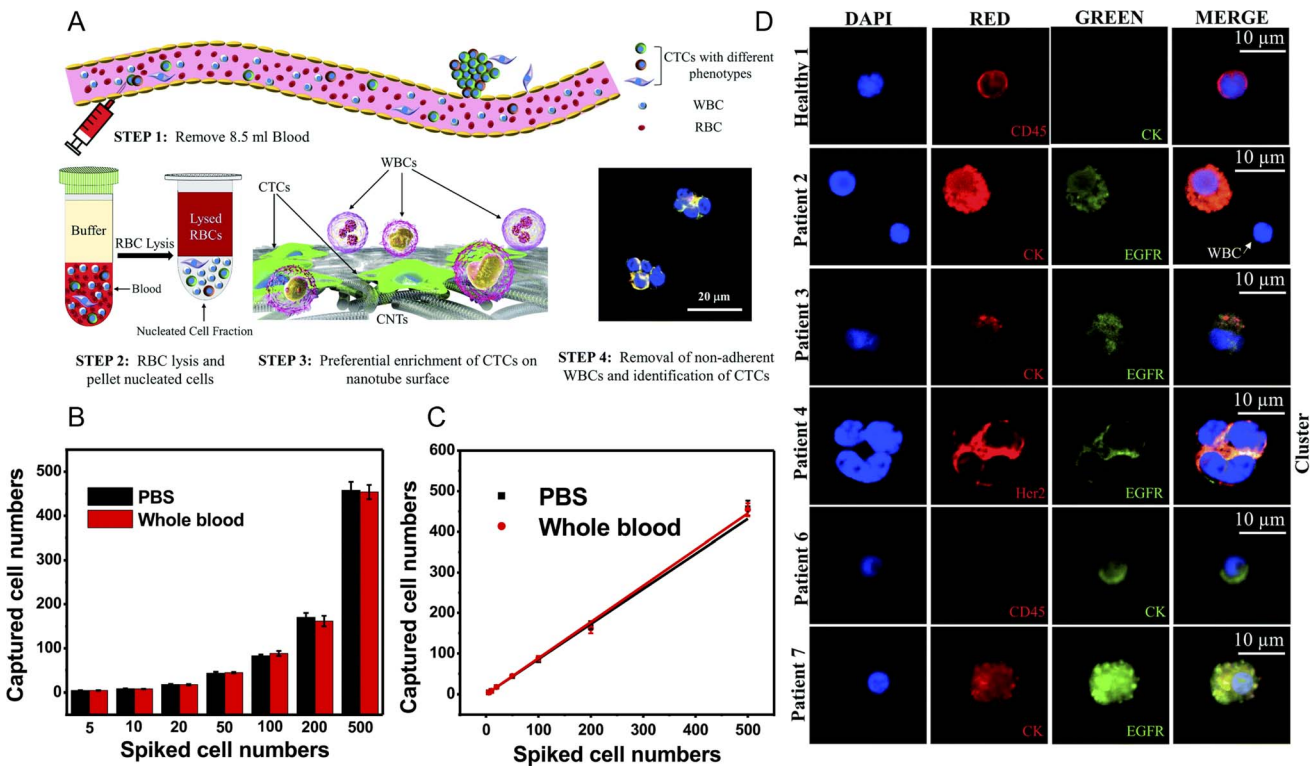

Fig. 4 (A) Steps to isolate and count CTCs using nanotube CTC chips.[52] (B) IMN capture efficiency for different MCF-7 concentrations (5–500 cells per ml) in PBS and whole blood. (C) Regression analysis of the number of captured cells against the number of MCF-7 cells in PBS and whole blood.[9] (D) Isolation of heterogeneous CTCs from breast cancer patients: CTCs were isolated from breast cancer patients based on CK, Her2 and EGFR. No CTCs were found in healthy controls. Blood volume: 4 ml and 8.5 ml. CK^+, $CD45^-$, $DAPI^+$ were identified as CTC, while $CD45^+$ and $DAPI^+$ were identified as WBC.[52] This figure has been adapted/reproduced from ref. 67 and 68 with permission from Elsevier and Royal Society of Chemistry, copyright 2021.

In principle, *in vivo* imaging allows dynamic tracking of tumor cells in a diagnostic setting and is used for detection and treatment, such as screening the effect of drugs on the number of CTCs in the blood. Optical coherence tomography (OCT) is a low loss, high resolution, non-invasive medical, imaging technique that can be used for cellular imaging along with significant scatter suppression techniques and high scattering contrast agents. Dutta *et al.* used large gold nanorods as contrast agents to detect individual tumor cells in the blood circulation using speckle modulated OCT.[51]

Lv *et al.* achieved efficient immunocapture and biocompatible site release of CTCs by combining the photothermal effect of gold nanorods with a thermally responsive hydrogel. By fabricating substrates to capture cancer cells by pre-embedding gelatin hydrogels in gold nanorods, the temperature-responsive gelatin rapidly dissolves at 37 °C, enabling the recovery of captured CTCs in large quantities and detection.[72] Fan *et al.* fabricated a near-infrared photoresponsive TiO_2 nanopillar array (TNA) substrate for efficient CTC capture and release. The substrate was coated with gelatin films doped with gold nanorods and could be used to capture and detect CTC by exploiting the temperature-sensitive properties of gelatin and the photothermal effect of GNR, and the captured cells could be released under NIR illumination.[73]

3.2.2 Gold nanospheres. Another gold nanostructure is gold nanospheres, which have received a lot of attention as photothermal therapeutic particles due to their excellent biocompatibility, chemical stability and ease of synthesis, and their ability to convert absorbed light energy into heat by having strong absorption tunable in the near-infrared region -shell structure. Under 808 nm laser irradiation, gold nanospheres aggregated inside the silica could significantly enhance its photothermal effect.[74] Li *et al.* used branched polyethyleneimine (PEI) as a linker to conjugate indocyanine green (ICG) on hollow gold nanospheres, thus providing a payload on the gold nanospheres as well as a cover layer with an appropriate thickness, and the conjugation of ICG led to a significantly higher plasma absorption of the composite structured material in the near-infrared region than that of the gold nanospheres alone. Thus, the photothermal conversion efficiency under NIR light irradiation was significantly improved.[75] Effectively improve the efficiency of tumor detection and treatment.

3.3 Carbon-based nanomaterials

Carbon-based nanomaterials, mainly carbon nanotubes and graphene, have been widely used for cancer photothermal applications. Carbon is a basic constituent element of the human body and has good biocompatibility. Carbon-based materials have strong optical absorption and high photothermal conversion efficiency in the near-infrared region due to their unique structure and high stability.[76] Carbon nanomaterials with photothermal properties show strong advantages in CTCs detection.

3.3.1 Carbon nanotubes. Carbon nanotubes (CNTs) are a versatile class of materials with very strong mechanical, thermal, electronic and biological properties that are used to detect tumors or kill cancer cells. Loeian *et al.* reported the isolation of highly pure tumor-derived epithelial cells (CTCs) from peripheral blood by exploiting the physical mechanism of preferential adhesion of CTCs to the nanotube surface. Carbon nanotubes were combined with microarray fabrication techniques for the capture and isolation of circulating tumor cells. Enrichment was first performed using an erythrocyte lysis protocol, and then the enriched samples were processed using nanotube CTCs chips to preferentially adhere CTCs to the nanosurface and counted with >90% adhesion and 100% tracking of carbon nanotubes[52] (Fig. 5). Zhu *et al.* constructed a colorimetric probe by modifying three DNA sequences (mDNA) onto Fe_3O_4 immunomagnetic nanoparticles (IMN) using the peroxidase-like activity and nonspecific DNA sequence effects of single-walled carbon nanotubes (SWCNT), which can detect tumor cells in blood with high selectivity, combining CTCs capture and detection, relative to other the method improved the sensitivity of detection and saved time.[9] In addition, Hevia *et al.* found that multi-walled carbon nanotubes may also have a "derivative effect" that eliminates tumor cells that sustain cancer cell growth, invasion, and metastasis, showing additional attractive detection and therapeutic advantages.[77] Xiao *et al.* utilized the single-walled carbon nanotubes to absorb near-infrared light which played dual roles of detecting CTCs first through their powerful Raman signal and then ablating breast cancer cells using their photothermal properties.[78] Also, carbon nanotubes were combined with gold nanoflowers for targeted diagnostics and selective photothermal therapy. Both photothermal and Raman properties of carbon nanotubes were greatly improved by forming nanocomposites with other materials, which can be helpful for cancer detection and treatment.[79]

3.3.2 Graphene materials. Graphene nanomaterials, as classical two-dimensional nanomaterials with unique structures and excellent physicochemical properties, show great potential for tumor cell detection and cancer therapy. Multifunctional graphene and graphene oxide play an important role in medicine, materials science, oncology, and biology as an emerging platform for CTCs capture and analysis due to their optical and electronic properties, high specific surface area, and ease of chemical synthesis and functionalization. Detection and isolation of CTCs from blood, which is essential to address early cancer detection, using graphene nanomaterials-based technology can significantly improve CTCs capture efficiency, and therefore, detection and utilization of CTC-derived molecular markers are critical in tumor cell detection and therapeutic processes.[80] Jiain *et al.* proposed a surface-enhanced Raman scattering (SERS) nanosilver complex equipped with a SERS nanosilver containing gold-integrated with anti-ErbB2 antibody graphene (hybrid-rGO@anti-ErbB2) for SERS-assisted CTC quantification. Compared to immunoaffinity-based CTC separation platforms, the centrifugal force-based SERS nanosilver filter sensor system was able to rapidly isolate up to 5 tumor cells per ml of live breast cancer cells from whole blood with high sensitivity and ease of use.[81] Zhang *et al.* developed an immuno-graphene oxide (GO) magnetic bead-based complex for sensitive, rapid, portable and low-cost detection of cancer cells. Efficient cell capture and highly sensitive photothermal detection can be realized simultaneously. Temperature changes induced by laser irradiation of GOs are used to establish

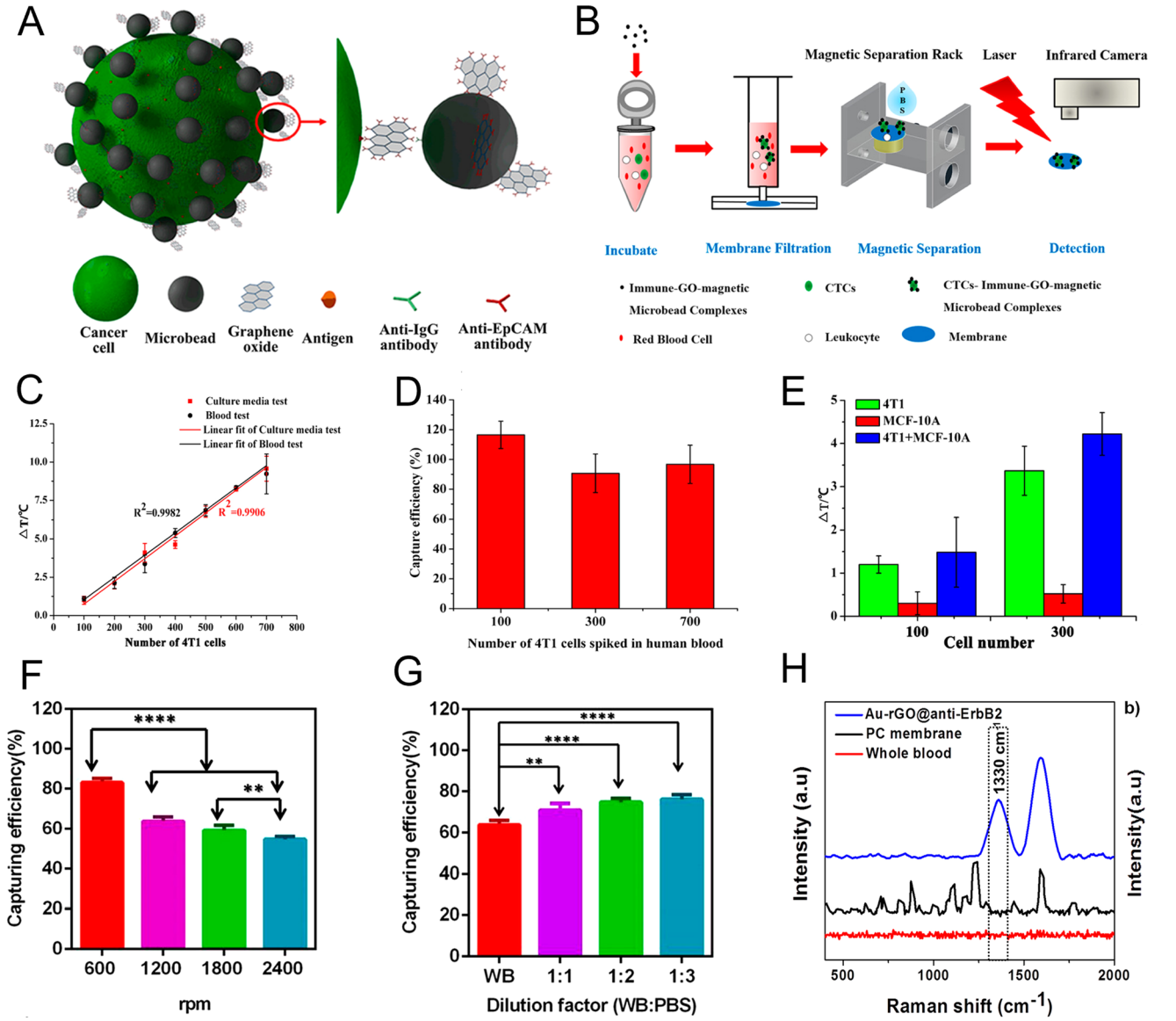

Fig. 5 (A) Schematic diagram of the complex recognizing cancer cells. (B) Immunomagnetic bead-based cell capture and photothermal detection process. (C) Standard curves for ΔT and 4T1 cell counts in culture medium and human blood. (D) Detection of added 4T1 cells in human blood. (E) Specificity assessment: 4T1 cells (green), MCF-10A cells (red), and a mixed sample of 4T1 and MCF10A cells (blue).[82] (F) Effect of centrifugation speed on CTCs counting capture efficiency. (G) Quantitative assessment of the effect of dilution on the capture efficiency of CTCs counting. (H) SERS spectral comparison between Au-rGO@anti-ErbB2 nanotag, PC membrane, and whole blood.[81] This figure has been adapted/reproduced from ref. 81 and 82 with permission from American Chemical Society, copyright 2016 and 2021.

a standard curve of temperature change *versus* the number of cancer cells[82] (Fig. 5).

3.4 Molybdenum-based nanomaterials

Molybdenum nanostructures, similar to other metal–semiconductor nanostructures, have a high photothermal conversion efficiency and a strong absorption of near-infrared light. Cells produce reactive oxygen species during metabolism, and H_2O_2 is one of them. H_2O_2 is overexpressed in tumor cells, and H_2O_2 plays a crucial role in many physiological processes such as cell signaling and apoptosis.[83] Molybdenum disulfide is stable and easily functionalized. The structure of monolayer MoS_2 consists of two layers of sulfur and one layer of molybdenum. The atoms are covalently bonded to each other in a sandwich structure. Hu *et al.* developed a sensitive sensor for detecting H_2O_2 discharge in tumor cells using MoS_2–Au–Ag nanocomposites to achieve high electrical conductivity and increase the surface area of the electrode, and the developed MoS_2 Au–Ag electrode exhibited excellent simulated enzymatic electrocatalytic activity during H_2O_2 oxidation. The sensor significantly improved the detection signal, resulting in a low detection limit, a wide detection range, and high selectivity and sensitivity for cancer detection by detecting H_2O_2 released from circulating tumor cells.[84]

Wang *et al.* introduced a near-infrared photoswitchable bioplatform for specific capture of CTCs through PEG–MoS_2

nanoflakes@gelatin nanocomposites and then introduced MUC1 aptamer as a specific recognition element by coupling reaction between aptamer and gelatin, and released the captured cells under 808 nm laser irradiation for recognition, capture, release and detection of different types of CTCs.[85]

3.5 Silica nanomaterials

Fluorescence is a frequently used tool for CTC detection, and epithelial antigens overexpressed on CTCs are detectable targets. Silica has a strong fluorescence capability, which is enhanced by combining biochips and shape control to detect CTCs. Sobhanan *et al.* reported the efficient detection and collection of blood by combining stem cell antigen (CD44)-specific immunosilica particles and immunofluorescent quantum dots with spectroscopic and time-resolved single photon counting using the selective attachment of cancer cells to silica particles. tumor cells in the sample. It was able to accurately identify 1–10 cancer cells out of 100 cancer cells in 1 ml blood sample.[86] Cui *et al.* developed a biochip for efficient detection of CTCs after modification of epithelial cell adhesion molecule antibodies (anti-EpCAM), using microfrosted slides and silica nanowires to improve detection efficiency (Fig. 7). The chip showed specificity and high capture efficiency of 85.4 ± 8.3% for prostate cancer cell line (PC-3) and has been successfully applied to identify CTCs from whole blood samples of prostate cancer patients.[54] Magnetic mesoporous silica nanoparticles (M-MSNs) are an ideal material for immunomagnetic separation and detection of CTCs, and can significantly improve the capture of CTCs with by designing fluorescent M-MSNs into spherical and rod-shaped forms, Chang *et al.* achieved efficient enrichment and fluorescence detection of CTCs in both the two

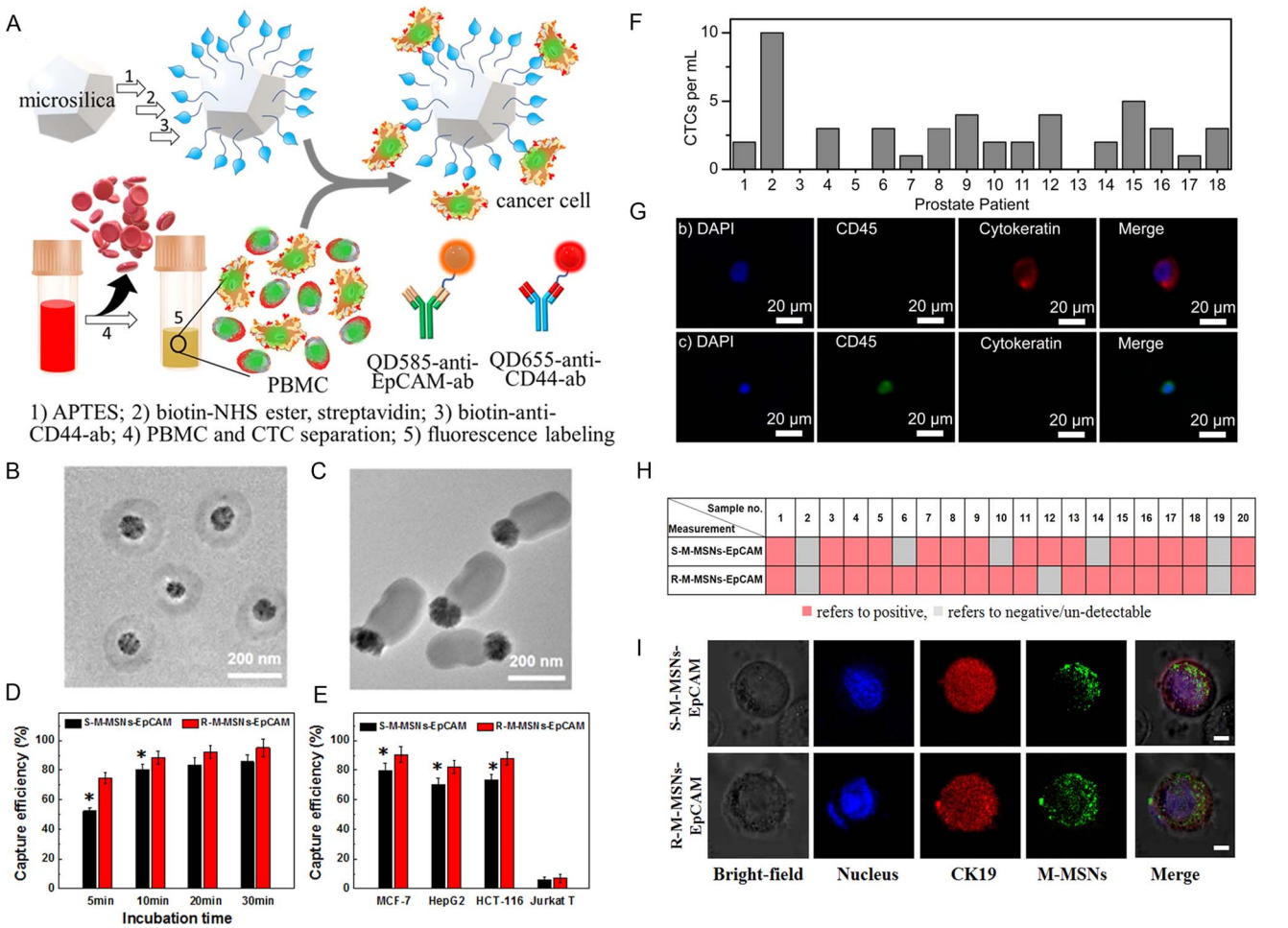

Fig. 6 (A) Scheme for functionalization of silica particles and isolation of cancer cells from blood samples[86] (this figure has been adapted/reproduced from ref. 86, with permission from Springer Nature, copyright 2022). (B) TEM images of spherical M-MSNs. (C) TEM images of rod-shaped M-MSNs. (D) Efficiency of capturing MCF-7 cells in whole blood at different incubation times. (E) Capture efficiency of adding four different types of tumor cells to whole blood: MCF-7, HepG2, HCT-116, and Jurkat T cells.[87] (F) Detection of CTC capture efficiency from 20 breast cancer patient blood samples containing CTCs. (G) Fluorescence images of CTCs captured with different shapes of M-MSNs-EpCAM from clinical blood samples of CTC-containing breast cancer patients. Red fluorescence represents CTCs ($CK19^+$) cells, green fluorescence represents MMSNs EpCAM, and the scale bar represents 5 μm.[54] (H) Number of CTCs captured in 1 ml of blood with anti-EpCAM-modified Fr-S-SNW2. (I) Typical fluorescence image of CTCs showing cytokeratin-positive CTCs with red fluorescence for counting ($DAPI^+/CD45^-/CK^+$). Typical fluorescence image of leukocytes showing CD45-positive leukocytes with green fluorescence for counting ($DAPI^+/CD45^+/CK^-$).[54] This figure has been adapted/reproduced from ref. 87 and 54 with permission from American Chemical Society, copyright 2018.

different shapes of M-MSNs-EpCAM obtained after binding to EpCAM antibodies (Fig. 6). Compared with the spherical M-MSNs, the rod-shaped M-MSNs had faster immunomagnetic separation and showed better performance in the separation and detection of CTCs in real clinical blood samples.[87]

Silicon dioxide is often used in combination with other materials, most commonly mesoporous silica nanoshells. These composites not only have better photothermal and fluorescent properties, but also the ability of drug loading. Xiao *et al.* designed a silicon dioxide microfiber combined with Au@Ag_2S nanomaterials, which enhanced the sensitivity of the sensor to temperature and was able to distinguish hepatocellular carcinoma cells from normal cells and kill the cancerous cells by photothermal heat.[88] Yin *et al.* used mesoporous silica as an intermediate layer and ferric iron tetroxide as the core, and CdTeS quantum dots as fluorescent labeling agent, which can detect and destroy cancer cells more perfectly.[89] Of course the coupling of silica and gold nanomaterials is very common, Seo *et al.* synthesized GNR@SiO_2 nanoparticles to enhance their near-infrared light absorption. The powerful photothermal and Raman properties were utilized to achieve synergistic effects of detection and therapy.[90]

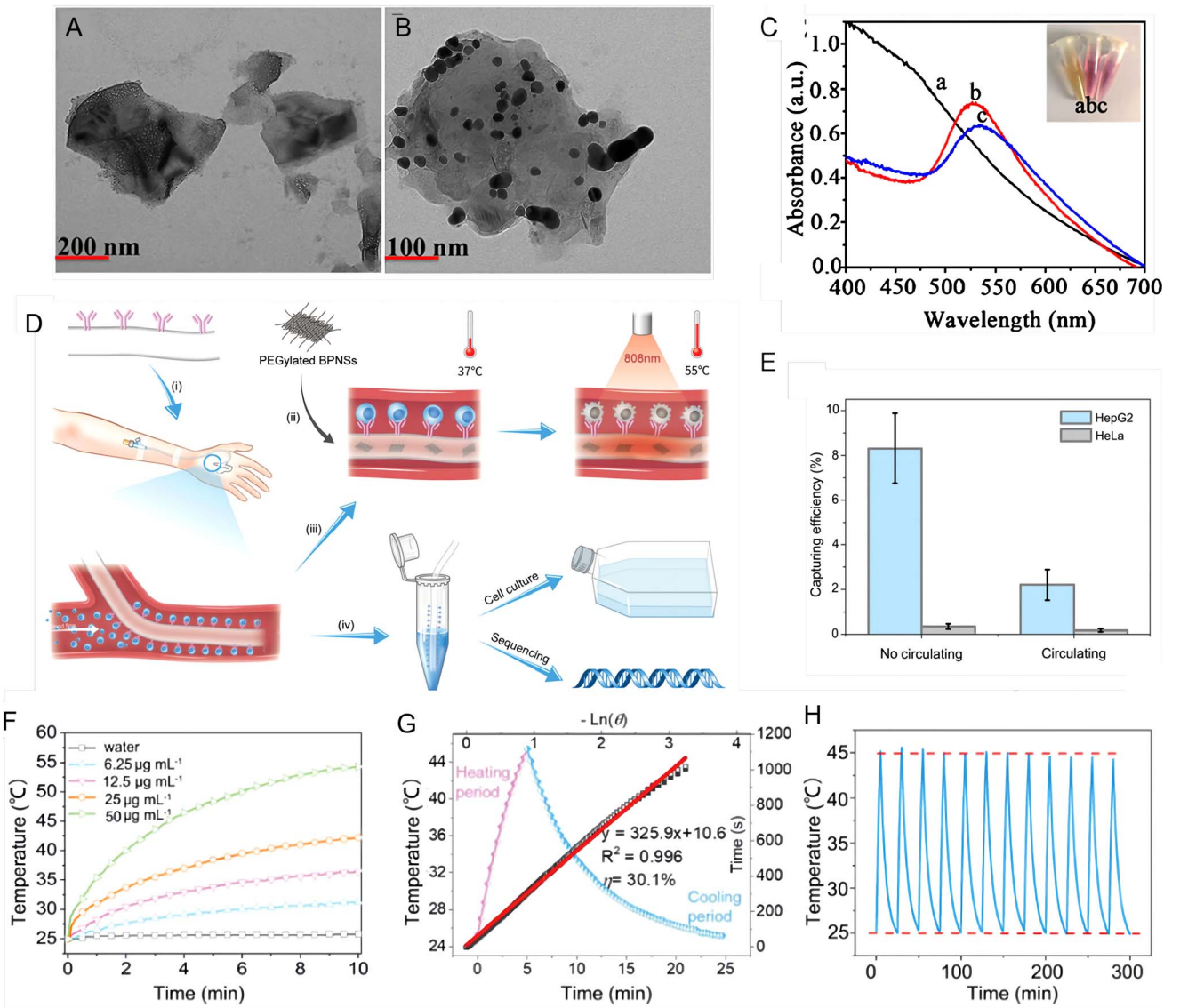

Fig. 7 (A) TEM images of BP nanosheets. (B) Transmission electron microscopy image of BP@AuNP nanohybridization. (C) UV-Vis spectroscopy analysis of (a) BP nanosheets (b) BP@AuNP nanohybrids (c) BP@AuNPs@aptamers. The inset shows digital photographs of the corresponding solutions.[57] (D) Schematic diagram of BPNSs catheter treatment. The anti-EpCAM antibody-functionalized catheter was first placed into the vein, then the polyethylene glycolized BPNSs were injected inside the catheter, and finally the catheter temperature was raised to 55 °C by exposure to 808 nm NIR to kill CTCs. (E) Cell capture efficiency under no circulation and circulation conditions. (F) Photothermal activities of the PEGylated BPNSs dispersed in aqueous solution at varied concentrations (0, 6.25, 12.5, 25, and 50 μg ml^{-1}) at a power density of 1 W cm^{-2}. (G) Determination of the photothermal-conversion efficiency at 808 nm. (H) Real-time temperature curves of PEGylated BPNS in aqueous solution for twelve laser ON/OFF cycles. For each cycle.[56] This figure has been adapted/reproduced from ref. 56 and 57 with permission from Springer Nature and John Wiley and Sons, copyright 2020.

Table 2 Some previously reported photothermal materials for CTC detection[a]

Materials	Concentration	Excitation wavelength	Surface coating/targeting	Advantages and disadvantages	Ref.
Ag–AgCl@Au	200 μg ml^{-1}	808 nm	FA	Dual pressure and temperature detection	67
Ti_3C_2@Au@Pt	500 μg ml^{-1}	808 nm	MUC1	Adoption of multi-adaptor recognition and binding	95
GO-magnetic microbead	100 μg ml^{-1}	808 nm	Anti-EpCAM	Higher detection limit and smaller range	82
Large gold nanorods	2.5 nM	835 nm	Anti-EpCAM	Dynamic detection	51
Ag_2S	100 μg ml^{-1}	795 nm	SA-HM	High binding capacity to CTC	53
BPNSs	5 mg ml^{-1}	808 nm	Anti-EpCAM	Capable of enriching and killing CTC	56
BP@AuNPs	400 μg ml^{-1}	530 nm	Anti-EpCAM	Lower detection limit	57
GNRs	40 μM	980 nm	Anti-EpCAM	Single-cell capture using microfluidic chips	96
TiO_2-GNR	100 μM	808 nm	Anti-EpCAM	Difficult to achieve high concentration capture using substrate	73
$Cu_3(PO_4)_2$	500 μg ml^{-1}	808 nm	PDA	Low specificity	66
MoS_2	125 μg ml^{-1}	808 nm	PEG	Low capture efficiency of high concentration CTC	85

[a] MUC1: polymorphic epithelial mucin; PDA: polydopamine.

3.6 Black phosphorus nanomaterials

Black phosphorus (BP) is a black crystalline with metallic luster and a semiconductor. Black phosphorus has become a hot research topic in the field of electronics and photochemistry due to its impressive carrier mobility. Phosphorus is one of the important elements accounting for about 1% of the total body weight, and black phosphorus has excellent biodegradability, low toxicity[91] and optical properties that have attracted much attention as a photothermal reagent for biomedical applications.[92] BP nanosheets have a large surface-to-volume ratio, easy surface functionalization, excellent biodegradability, and excellent photothermal conversion efficiency.[93] Liu *et al.* synthesized gold nanoparticles–anchored BP nanosheets (BP@AuNPs) by exploiting the strong chelating ability of phosphorus or phosphorus (P_xO_y species) oxides with gold nanoparticles to stabilize BP by *in situ* growth of AuNPs on BP. Meanwhile, P_xO_y species were generated by the strong chelating ability of Au with P_xO_y species and stabilized and reacted with molybdate to generate electrochemical currents, which improved the sensitivity of electrochemical detection. By combining functionalized BP nanosheets with magnetic nanobeads modified with antiEpCAM antibodies, a highly sensitive and selective sensor was made and applied to the efficient capture and sensitive detection of CTCs in whole blood.[57] Wang *et al.* developed an intravenous catheter for *in vivo* enrichment and photothermal killing of CTCs. The catheter surface was modified with an anti-EpCAM antibody and the interior was filled with black phosphorus nanosheets, as shown in Fig. 7 for a schematic diagram of this catheter treatment. CTCs in the peripheral blood is continuously captured by the catheter as it circulates. This catheter was able to capture 2.1% of EpCAM and CTCs in just 5 minutes[56] (Fig. 7).

3.7 Other nanomaterials

In addition to the above commonly used photothermal materials, there are many nanomaterials used to detect CTCs, such as copper and silver, *etc.* Luo *et al.* proposed a sensitive and reliable photoelectrochemical (PEC) biosensor with magnetic Fe_3O_4 nanospheres (MNs) and Cu_2O nanoparticles (Cu_2O-NPs) for efficient magnetic trapping and signal amplification of CTCs, respectively. The Cu_2O aptamer probe absorbs excitation light when bound to the CTCs surface, and the photocurrent intensity is further reduced to effectively detect CTCs. Ding *et al.* developed a nanoplatform for efficient separation and ultrasensitive detection of CTCs by combining NIR multivalent aptamer-functionalized Ag_2S nanodots with hybrid cell membrane-encapsulated magnetic nanoparticles. Due to the cell membrane modification and magnetic separation, CTCs detection is sensitive and resistant to interference.[53] Ding *et al.* used tannic acid (TA)-functionalized magnetic nanoparticles (MNP) to efficiently separate heterogeneous CTCs from patient blood samples. This method inhibits nonspecific adhesion of individual nucleated cells in peripheral blood and enhances CTCs capture efficiency.[58] Cai *et al.* synthesized novel branched PtAuRh trimetallic nanospheres (bPtAuRh-TNS) with huge specific surface area and excellent catalytic activity for the detection of CTCs in clinical blood samples using anti-EpCAM antibodies as capture probes.[94] The use of these materials greatly improved the efficiency of CTCs detection. Table 2 lists some of the some of the previously reported photothermal materials used for CTC detection, most of which are mentioned throughout this paper.

4. Summary and outlook

Over the past few years, photothermal materials have been gradually used in CTC detection. These photothermal nanomaterials are capable of converting radiant light energy into thermal energy under near-infrared light irradiation, which plays a significant role in cancer tumor detection and treatment. Such as gold, carbon, molybdenum, silicon and phosphorus. The photothermal performance of these photothermal materials can be improved by adjusting their shapes, sizes, and

doping with other elements, and the composite of multiple materials makes them more advantageous and efficient in CTC detection. For example, gold-based nanomaterials are widely used in the biomedical field due to their good photothermal and catalytic properties, as well as one of the shape and size variability. Materials like carbon, molybdenum, and phosphorus, although inferior to gold nanomaterials in some aspects, can greatly improve the photothermal and catalytic properties of the materials by combining them with gold nanoparticles, and achieve the purpose of detecting CTCs by modifying the targeting substances on the surface.

Currently, the use of photothermal materials in CTC detection faces many challenges at the clinical stage, such as reaction time, photothermal efficiency, capture efficiency, and sensitivity. A major issue that exists is specificity, and the ability to capture CTC accurately and efficiently is a major challenge. Whether using antibodies or substrates or other methods for capture is quite challenging. Most of the literature uses anti-EpCAM antibodies to target CTCs, but there is no guarantee that CTCs will be captured completely, since some cells will still be lost, so this is an aspect that should be investigated in the future. Simplicity and portability should also be considered, complex experimental procedures can easily lead to errors. The biosafety of the materials should not be neglected, while considering the photothermal properties of these photothermal nanomaterials, therefore attention should also be paid to their biocompatibility and biotoxicity. In the future, multiple methods should be combined for CTC detection, such as photothermal and electrochemical combination, photothermal and fluorescence combination, *etc.*, to improve the specificity and sensitivity of the materials. Although most of the photothermal materials are currently used in the field of cancer treatment, they can also be used in the field of CTC detection through improvement, and these photothermal materials can be of significant help in the early screening and later treatment of cancer, and widely used in the future for cancer diagnosis and treatment.

Conflicts of interest

There is no conflict to declare.

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