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REVIEW

iRADIOLOGY

Optical imaging of in vivo adoptive T-cell therapy: State of the art and challenges

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Abstract

Adoptive T-cell therapy (ACT), which is an important type of live cell therapy, has achieved unprecedented success in treating hematological malignancies. Recent studies have shown that ACT is also a promising treatment for solid tumors. Visualizing the in vivo fates (distribution, homing, infiltration, proliferation, and exhaustion) of the immune cells used for ACT (ACT immune cells) is of great importance to promote basic research and clinical translation of ACT. Optical imaging techniques, including bioluminescence, fluorescence, and photoacoustic imaging, have the advantages of high sensitivity, high spatiotemporal resolution, minimal exposure to harmful radiation, and simple instrumentation. Recently, various types of optical imaging probes, including bioluminescence, fluorescence, and photoacoustic imaging probes, have been used to visualize ACT immune cells in vivo and evaluate the molecular mechanism, efficacy, and side effects of ACT. In this review, the optical imaging probes and labeling methods that have been used for in vivo visualization of ACT immune cells are summarized, and the opportunities and challenges of using optical imaging to visualize ACT immune cells in vivo are discussed.

KEYWORDS
adoptive T-cell therapy, bioluminescence imaging, fluorescence imaging, immunotherapy, optical imaging, photoacoustic imaging

Abbreviations: ACT, adoptive T-cell therapy; ACT immune cells, immune cells used for ACT; CAR T-cells, chimeric antigen receptor-modified T-cells; CTLs, cytotoxic T lymphocytes; EPR, enhanced permeability and retention; FDA, United States Food and Drug Administration; FFZ, fluorofurimazine; FITC, fluorescein 5-isothiocyanate; GraB, granzyme B; MRI, magnetic resonance imaging; NIRF, NIR fluorescent; NIR-I, first near-infrared window; NIR-II, second near-infrared window; PET/CT, positron emission tomography/computed tomography; TCR T-cells, T cell receptor gene-modified T-cells; TILs, tumor-infiltrating lymphocytes.

1 | INTRODUCTION

Cancer immunotherapy is an advanced treatment that uses the body's own immune cells to kill cancer cells. Its history dates back to the late 19th century when it was observed that some cancer patients experienced symptom relief after viral infections [1]. In the 20th century, scientists explored the functions of T-cells and B-cells, and demonstrated the molecular mechanism whereby immune checkpoints inhibit T-cell activity [2]. In the 21st century, the first immune checkpoint inhibitor, ipilimumab, was approved by the United States Food and Drug Administration (FDA), marking the beginning of a new era in the history of cancer immunotherapy (Figure 1) [3]. In 2017, the first CAR T-cell therapy, a treatment using chimeric antigen receptor-modified T-cells (CAR T-cells), was approved by the FDA for treatment of acute lymphoblastic leukemia in children and adolescents, opening the door of cellular immunotherapy [4]. In 2018, immunotherapy pioneer Professors James P. Allison and Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine for their discovery that immune checkpoint inhibition acts as a cancer therapy, sparking a frenzy of research on cancer immunotherapy [5].

In accordance with their therapeutic mechanisms, cancer immunotherapies are classified into four categories: immune checkpoint inhibitor therapy, adoptive T-cell therapy (ACT), vaccine therapy, and cytokine therapy [6]. In recent years, ACT has received considerable attention from academic and industry researchers because of its high specificity and ability to kill cancer cells directly [7]. ACT uses various types of immune cells, including tumor-infiltrating lymphocytes (TILs), cytotoxic T lymphocytes (CTLs), CAR T-cells, and T-cell receptor-modified T-cells (TCR T-cells) (Figure 2). To date, eight T-cell-based therapies have been approved by the FDA for cancer treatment [8]. Compared with gene-based, immunomodulatory, small-molecule chemical, and large-molecule antibody-based drugs, the immune cells used for ACT (ACT immune cells) have completely different in vivo fates, which include their in vivo distribution, homing, infiltration, proliferation, and exhaustion, because they are living cell-based drugs [9]. In vivo visualization of ACT immune cells is critical for clinical translation of ACT.

Several imaging modalities, including positron emission tomography/computed tomography (PET/CT), magnetic resonance imaging (MRI), and optical imaging, have been used for in vivo visualization of ACT immune cells [14, 15]. PET/CT, which has high sensitivity and the ability to penetrate deep tissues, has been used to assess the in vivo distribution and homing of ACT immune cells and therapeutic efficiency of ACT [16]. Some reviews have summarized the advances in PET/CT imaging of ACT immune cells [17–19]. MRI has also been used for in vivo visualization of ACT immune cells because it has high resolution and employs non-ionizing radiation [20, 21]. However, its sensitivity is low and its image-processing time is long, limiting its use for in vivo tracking of ACT immune cells. Compared with PET/CT and MRI, optical imaging, such as bioluminescence, fluorescence, and photoacoustic imaging, has the advantages of high sensitivity, high spatiotemporal resolution, minimal exposure to harmful radiation, and low

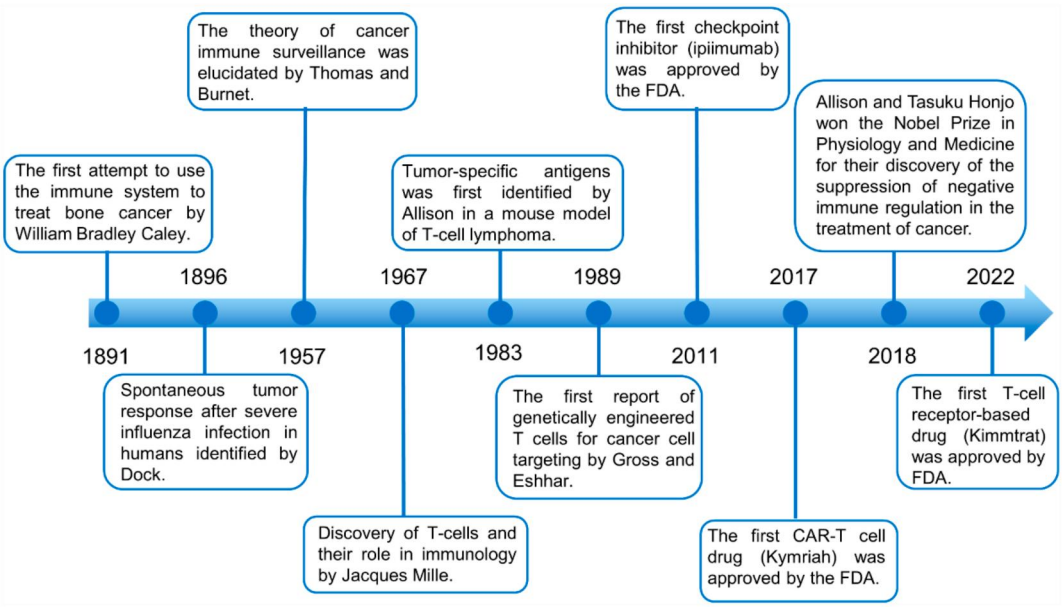

FIGURE 1 History of cancer immunotherapy [2–5].

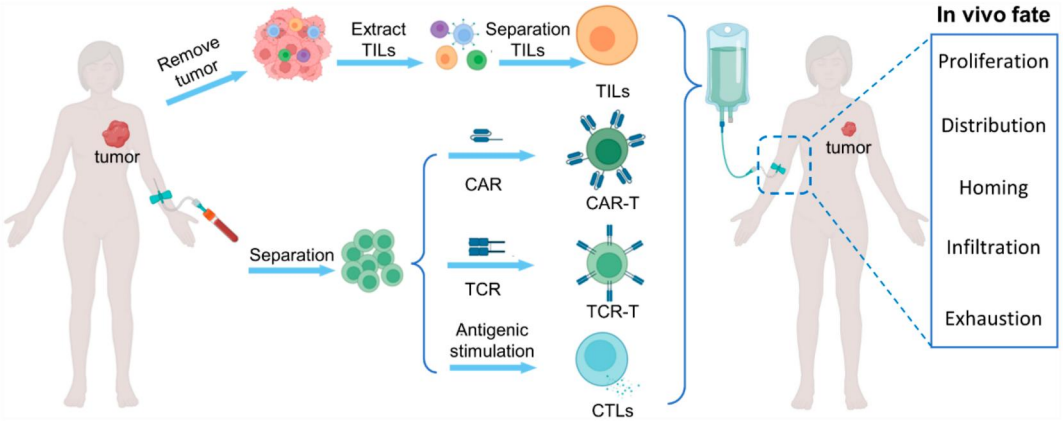

FIGURE 2 Various types of immune cells used for adoptive T-cell therapy [6–13]. *Source*: Created with BioRender.com.

costs [22]. In recent years, optical imaging has been widely used in preclinical studies to visualize ACT immune cells in vivo [23] because it reveals in vivo fates, such as infiltration of immune cells, unlike PET/CT and MRI [24]. Therefore, optical imaging promotes clinical translation of ACT. Various types of optical imaging probes and labeling methods have been developed for in vivo bioluminescence, fluorescence, and photoacoustic imaging of ACT immune cells. In this review, we summarize the recent advances in the application of optical imaging to in vivo visualization of ACT immune cells, focusing on optical imaging probes and labeling methods that have been used for in vivo visualization of the cells. Moreover, we discuss the opportunities and challenges of using optical imaging for in vivo visualization of ACT immune cells.

2 | CLASSIFICATIONS OF OPTICAL IMAGING PROBES

Optical imaging probes used for in vivo visualization of ACT immune cells are classified into three categories by the mechanisms that generate optical signals: bioluminescence, fluorescence, and photoacoustic imaging probes [25]. The probes used for bioluminescence imaging of ACT immune cells are generally produced by forcing cells to express luciferase enzymes that catalyze oxidation of substrates, such as luciferin, to generate luminescent signals [26]. Fluorescence imaging probes are classified into three categories according to their materials: small-molecule fluorescent probes, fluorescent nanoprobes, and activatable nanoprobes. The range of emission wavelengths of fluorescence imaging probes covers the first near-infrared (NIR-I) region (650–950 nm) and the second near-infrared (NIR-II) region (1000–1700 nm) [27, 28]. Fluorescence imaging in the NIR-II region has a deeper penetration depth and less scattering compared with that in visible and NIR-I regions, which has made it a focus point in recent years [10, 29, 30]. These probes are used for in vivo visualization of ACT immune cells through chemical conjugation, cellular internalization, and targeted molecular activation. Photoacoustic imaging of ACT immune cells relies on the absorption of pulsed laser energy by photoacoustic imaging probes to generate ultrasonic waves [31]. A hybrid imaging modality overcomes the limitations of a single imaging modality and provides complementary information on tissue structures and molecular functions. Some photoacoustic imaging probes have been used to evaluate the efficacy of ACT [32, 33].

2.1 | Bioluminescence imaging probes

In vivo survival and proliferation of ACT immune cells are critical for the efficacy of ACT. Visualizing the in vivo distribution, homing, and proliferation of ACT immune cells facilitates understanding of the therapeutic mechanism of ACT and predicting ACT efficacy [34, 35]. Endogenous bioluminescence imaging probes have stable expression characteristics across cell lines at various passage numbers, showing high sensitivity and high signal-to-noise ratios [36]. Therefore, they can reveal not only the in vivo distribution and homing of ACT immune cells but also the proliferation of the cells. Several bioluminescence imaging probes have been used in preclinical studies to visualize ACT immune cells in vivo [11, 28, 36]. Su et al. [11] prepared a probe for dual-color bioluminescence imaging by transfecting MG63.3 human osteosarcoma cells and B7-H3 CAR T-cells with Antares luciferase and AkaLuc luciferase, respectively. The biodistributions of tumor cells and CAR T-cells were visualized in the same mouse using delayed dual-color

bioluminescence imaging (Figure 3), which was enabled by the absence of cross-reactivity between the two luciferases and the short in vivo half-lives of the enzyme substrates. The authors also synthesized fluorofurimazine (FFZ) to replace furimazine, which is a substrate for NanoLuc luciferase, as the substrate for Antares. Antares is a highly sensitive luciferase formed by combining NanoLuc and CyOFP (an orange fluorescent protein). However, using furimazine as a substrate for Antares results in low-intensity bioluminescence because furimazine has poor water solubility and bioavailability. The water solubility and bioavailability of FFZ are better than those of furimazine. Therefore, using FFZ as the substrate for Antares improves the intensity of bioluminescence produced by the luciferase. The transfected B7-H3 CAR T-cells were intravenously injected into a mouse model of human osteosarcoma (the mice were injected with transfected MG63.3 human osteosarcoma cells), and their biodistribution, tumor homing, and therapeutic efficacy were evaluated by delayed bioluminescence imaging. Skovgard et al. [37] prepared a probe for dual-color bioluminescence imaging by genetically modifying M28z CAR T-cells and MSTO211h cells to express effLuc luciferase and ffLuc luciferase, respectively. In both in vitro and in vivo experiments, the authors demonstrated that the intensity of bioluminescence signals correlated positively to the numbers of effLuc-expressing M28z CAR T-cells and ffLuc-expressing MSTO-211h cells, providing the basis to quantify the numbers of CAR T-cells and tumor cells in vivo. They also observed that intravenously injected effLuc-expressing M28z CAR T-cells migrated to the lungs of normal and tumor-bearing mice before homing to tumor sites. Moreover, they found that the in vivo efficacy of CAR T-cell therapy was closely associated with the number of antigens expressed on the surface of tumor cells, providing the basis to optimize CAR T-cell therapy.

The above studies demonstrated the significant role of bioluminescence imaging probes in the in vivo visualization of ACT immune cells and provided directions for the development of new bioluminescence imaging probes. The following should be considered in the development of new bioluminescence imaging probes for in vivo visualization of ACT immune cells [38]: (i) the development of a highly active and non-toxic luciferase, (ii) the development of a highly water-soluble,

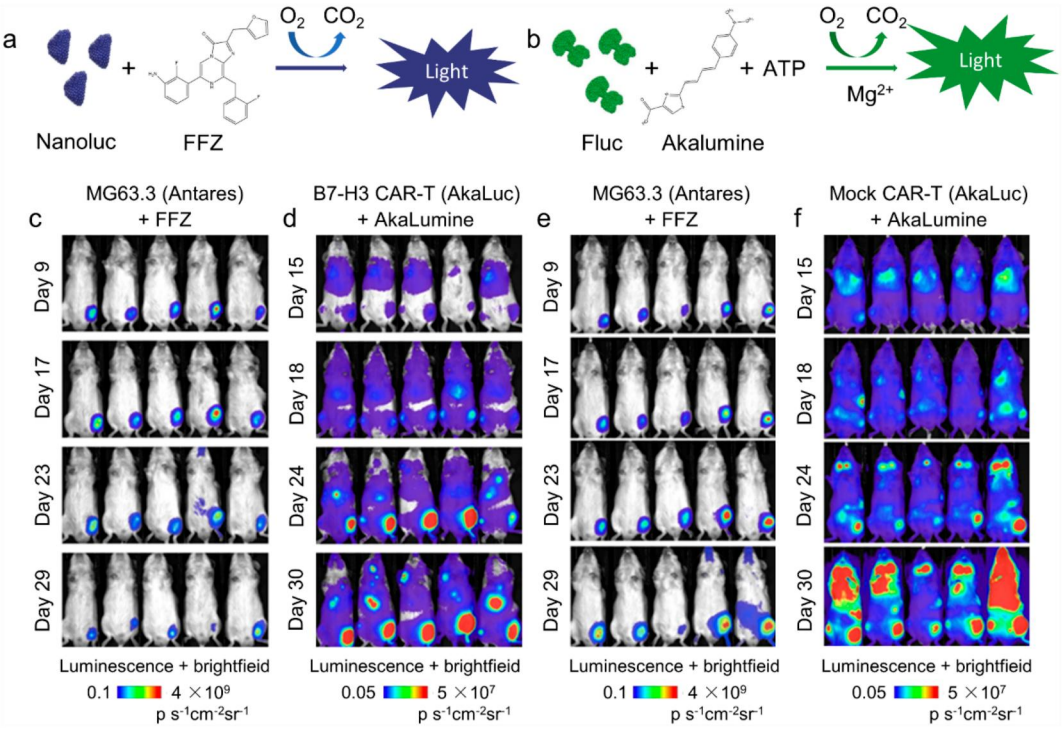

FIGURE 3 In vivo dual-color bioluminescence imaging of B7-H3 CAR T-cells and MG63.3 tumor cells. The generation of bioluminescence by (a) Antares-catalyzed oxidation of FFZ and (b) AkaLuc-catalyzed oxidation of Akalumine are shown. (c,d) Dual-color bioluminescence imaging of MG63.3 tumor cells and B7-H3 CAR T-cells in the same mouse. The tumor cells were visualized using Antares and FFZ, and CAR T-cells were visualized using AkaLuc and Akalumine. (e,f) Dual-color bioluminescence imaging of MG63.3 tumor cells and Mock CAR T-cells in the same mouse. Tumor cells were visualized using Antares and FFZ, and CAR T-cells were visualized using AkaLuc and Akalumine. Reproduced with permission [11]. Copyright © 2020, The Authors, under exclusive license to Springer Nature America, Inc. FFZ, fluorofurimazine.

bioavailable, and specific substrate for the luciferase, and (iii) stable expression of the luciferase in ACT immune cells [39]. Bioluminescence imaging probes have been mainly used for in vivo visualization of ACT immune cells in preclinical research because of their limited imaging depth and complicated preparation. The development of bioluminescence imaging probes with high sensitivity, long emission wavelengths, and low biotoxicity is an important direction for future research [40, 41].

2.2 | Small-molecule fluorescent probes

Small-molecule dyes are important reagents in fluorescence imaging of ACT immune cells. Various small-molecule fluorescent probes have been developed, and some of them have been commercialized, including fluorescein 5-isothiocyanate and cyanine [42]. The fluorescence emission wavelengths of these dyes cover the wavelength ranges of visible light (400–600 nm) and NIR-II [43]. Compared with endogenous bioluminescence imaging probes, small-molecule fluorescent probes have the advantages of a low molecular weight, low toxicity, and high fluorescence quantum yields [42]. They have been used in preclinical studies for labeling and in vivo visualization of ACT immune cells, macrophages, and dendritic cells [44].

Two methods of labeling immune cells with small-molecule fluorescent probes have been developed to visualize the in vivo fate of cells: direct and indirect labeling methods [44]. In the direct labeling method, carboxylated small-molecule dyes are directly coupled to the amino groups on the surface of immune cells by the amidation reaction, enabling probe labeling of living cells [45]. The method is simple and efficient, but it tends to reduce cell activity and functions. In the indirect labeling method, the surface of immune cells is labeled with functionalized reactive groups through a hydrophobic interaction or glycosylation reaction, and then the probes are coupled to reactive groups through biorthogonal reactions [45]. The reaction conditions for the indirect labeling method are mild, the efficiency of the method is high, and the labeling process does not interfere with the function of immune cells [46]. Therefore, the indirect labeling method has been widely used to label immune cells with small-molecule dyes in recent years. Kim et al. [10] used a two-step indirect labeling method to successfully label CTLs with small-molecule dyes (Figure 4). In the first step, CTLs and Ac4ManNAz were co-incubated for 24 h to anchor the N_3 group of AcManNAz to the surface of CTLs through Ac4ManNAz-mediated glycan metabolism. Then, the CTLs were co-incubated with DBCO-Cy5.5 for 10 min to attach DBCO-Cy5.5 to the anchored N_3 group through a bioorthogonal reaction. Two-step labeling was highly efficient and completed quickly under mild reaction conditions. After the labeling, the viability, proliferation, and function of CTLs were unaffected. The labeled CTLs were intravenously injected into ovalbumin-expressing mice bearing E.G-7 tumor cells and their in vivo distribution and infiltration were visualized for 30 days. The two-step indirect labeling method enables the use of small-molecule fluorescent dyes for in vivo visualization of ACT immune cells.

2.3 | Fluorescent nanoprobes

Compared with bioluminescence imaging probes and small-molecule fluorescent probes, fluorescent nanoprobes have the following advantages [47]: (i) a large surface area to volume ratio, which is beneficial for specific labeling of ACT immune cells; (ii) multimodal molecular imaging, which provides multi-scale information on ACT immune cells; and (iii) an enhanced permeability and retention (EPR) effect of the nanoprobes, which enhances the tumor-targeting efficiency of nanoprobes and the sensitivity of in vivo visualization of ACT immune cells.

Various types of fluorescent nanoprobes, including hybrid silicon, gold, and iron oxide nanoparticles, have been used to visualize the in vivo distribution, homing, and migration of ACT immune cells [48]. Harmsen et al. [12] prepared dual-modal NIR fluorescent (NIRF)/PET nanotags using fluorescent silicon nanoparticles labeled with ^{89}Zr nuclide ($t_{1/2}$ = 3.27 days) and used the nanotags to visualize the in vivo fate of hcEA-redirected CAR T-cells. The nanotags enabled hybrid imaging with the advantages of NIRF imaging (providing qualitative information on the entry of the nanotags into CAR T-cells) and PET imaging (providing quantitative information on the in vivo distribution of CAR T-cells). The CAR T-cells were labeled with nanotags through phagocytosis at a labeling efficiency of 82.6%. After labeling, the cells exhibited a high percentage of viability (up to 90%), demonstrating the low cytotoxicity of the nanotags in CAR T-cells. Furthermore, the NIR/PET nanotags resided in the labeled CAR T-cells for up to 7 days, enabling visualization of the in vivo distribution and migration of the cells. The method of administering the nanotag-labeled CAR T-cells (intravenous or intraperitoneal injection) to mice with peritoneal cancer influenced the in vivo distribution of the cells, suggesting that the method of administering CAR T-cells for treating solid tumors should be optimized. Moreover, leakage of

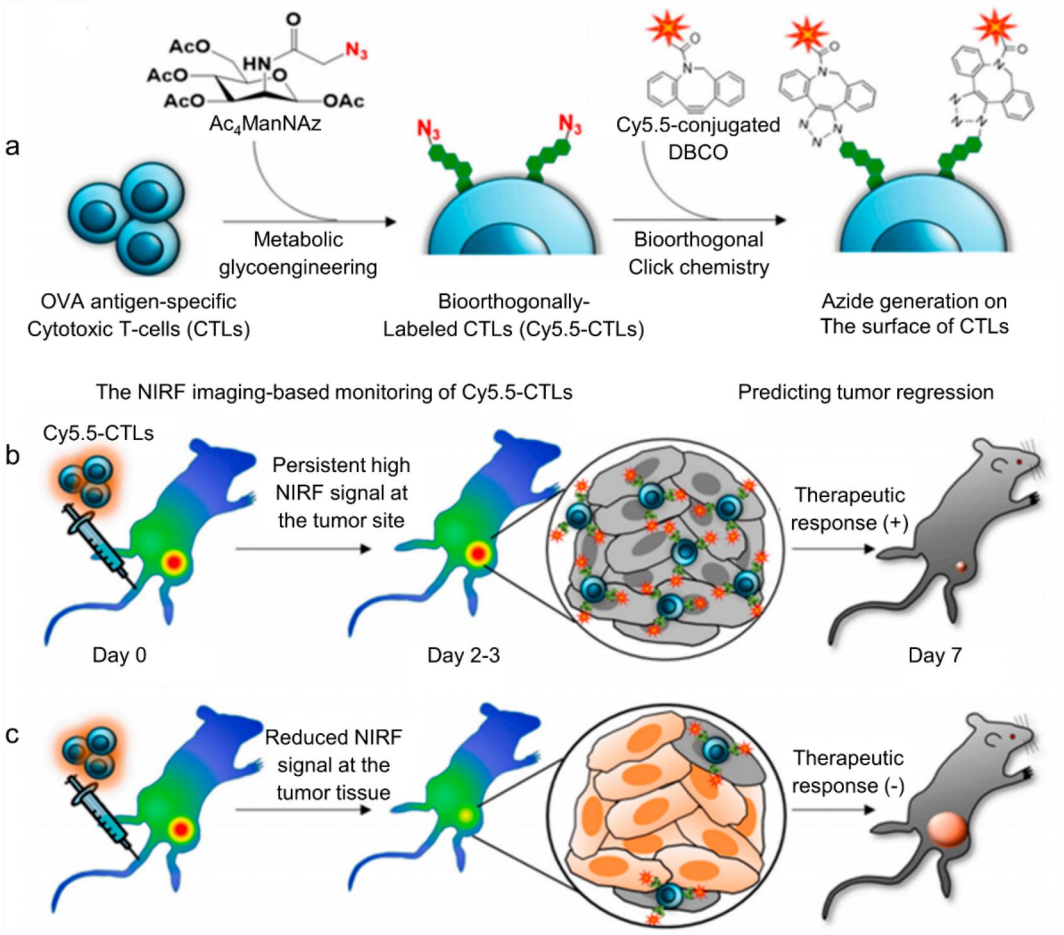

FIGURE 4 Labeling and monitoring of CTLs to predict the efficacy of ACT. (a) Preparation of Cy5.5-CTLs by biorthogonal labeling of ovalbumin (OVA)-antigen-specific CTLs with Cy5.5 dye. (b,c) Monitoring of NIR fluorescent signals generated by Cy5.5-CTLs at tumor tissues to predict the efficacy of ACT. Reproduced with permission [10]. Copyright © 2020 Elsevier B.V. ACT, adoptive T-cell therapy; CTLs, cytotoxic T lymphocytes.

the NIRF/PET nanotags from the labeled CAR T-cells and the decrease in the nanotag concentration with the proliferation of the cells limited the specificity and sensitivity of the in vivo visualization of the nanotag-labeled CAR T-cells (Figure 5). Zhang et al. [49] prepared cross linked iron oxide nanoworms (CLIO NWs) that were labeled with small-molecule fluorescent dyes and electrostatically attached them to the surface of CAR T-cells. The fluorescent nanoprobes facilitated long-term (72 h) visualization of the in vivo fate of CAR T-cells in NSG mice with leukemia. Furthermore, they enhanced the transduction efficiency of the CAR T-cells, providing a multifunctional nanoplatform to generate and track CAR T-cells.

Fluorescent nanoprobes visualize the in vivo distribution, migration, and infiltration of ACT immune cells after labeling the cells through cell internalization and chemical conjugation [50]. However, there are some shortcomings in the labeling of ACT immune cells with existing fluorescent nanoprobes. For example, nanoprobes cannot reflect the proliferation of cells because they are exogenous labels that may be effluxed by the cell. The efflux leads to non-specific labeling and decreases in the intensity of nanoprobe-generated fluorescent signals with the proliferation of cells. Moreover, the safety of nanoprobes should be assessed and optimized [51].

2.4 | Activatable nanoprobes

In addition to traditional nanoprobes, activatable nanoprobes have become attractive probes for in vivo visualization of ACT immune cells. Under normal conditions, activatable nanoprobes are in an "off" state. Therefore, no fluorescent signal is generated [7, 52]. However, after perforin or granzyme B (GraB) is released from ACT immune cells to kill cancer cells, the

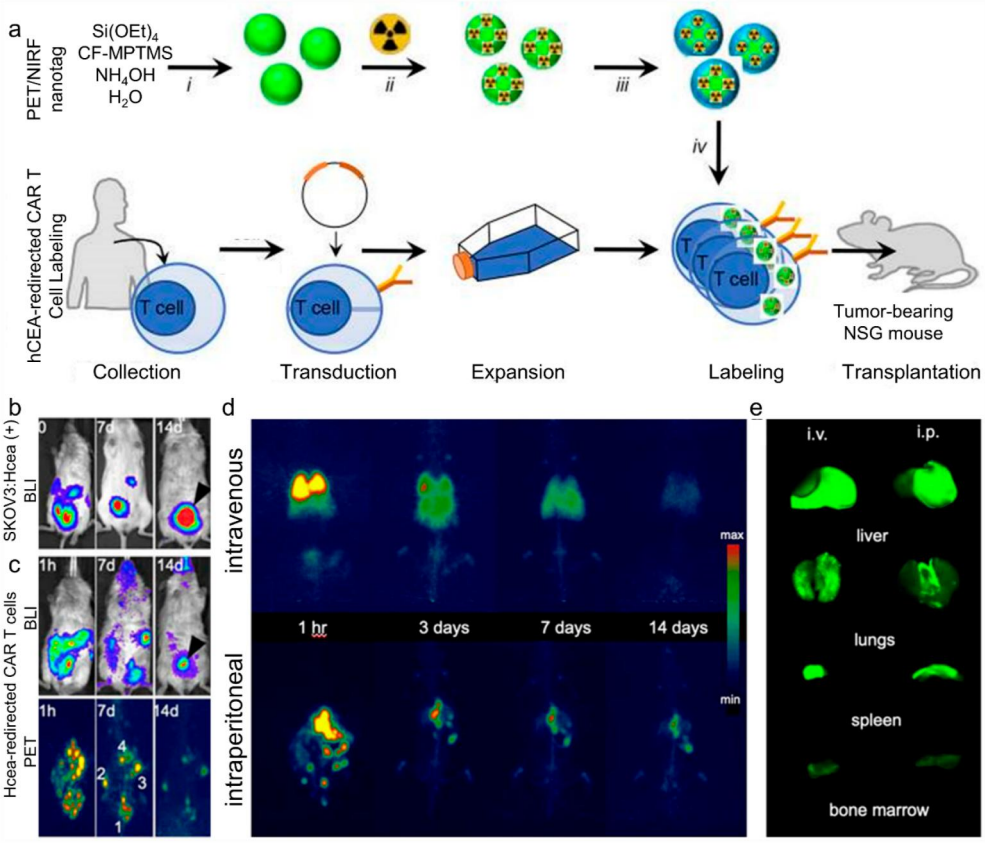

FIGURE 5 Monitoring of the in vivo distribution of CAR T-cells. (a) Preparation of hCEA-redirected CAR T-cells labeled with NIRF/PET nanotags. (b) Bioluminescence imaging of an NSG mouse before and after injection of SKOV3: hCEA (+) cells. (c) Bioluminescence and PET imaging of an NSG mouse after the administration of nanotag-labeled CAR T cells. (d) In vivo distribution of CAR T-cells at various time points. Cells were intravenously or intraperitoneally injected into an NSG mouse. (e) NIRF imaging of the major organs of the mouse intravenously or intraperitoneally injected with CAR T-cells. NIRF imaging was performed on day 14 after injection of the cells. Reproduced with permission [12]. Copyright © 2020 Elsevier Ltd. NIRF, NIR fluorescent.

nanoprobes are activated, leading to the generation of fluorescent signals [53]. Therefore, quantifying the intensity of fluorescent signals generated by activatable nanoprobes is an effective method to predict the in vivo expression level of perforin or GraB and the efficacy of ACT.

Several types of activatable nanoprobes, including peptide-based small molecular probes, macromolecular reporters, and semiconducting polymer nanoprobes (SPNPs), have been used to predict the in vivo expression level of GraB and the efficacy of ACT [54–56]. ACT immune cells do not need to be prelabeled with activatable nanoprobes, thereby greatly reducing the complexity of the imaging process. Zhang et al. [13] developed an SPNP for dual-modal NIRF/photoacoustic imaging of the infiltration and activation of CTLs (Figure 6). The SPNP was composed of an amphiphilic semiconducting polymer coupled to a GraB-cleavable peptide labeled with IR800 dye. It targeted a tumor region through the EPR effect, bypassing the relabeling of CTLs. When CTLs released GraB into the tumor, the SPNP reacted with GraB and released the dye-labeled peptide, resulting in a decrease in the intensity of NIRF and photoacoustic signals from the dye. The SPNP has been used to evaluate the efficacy of BEC (a small-molecule inhibitor of arginases I and II) in BALB/c mice bearing 4T1 tumors. However, because the generation of NIRF and photoacoustic signals depends on the activation of the SPNP, the signal-to-noise ratio of the nanoprobes was low. Xu et al. [57] synthesized a GraB-activated sonoafterglow nanoprobe (Q-SNAP) that generated an afterglow by ultrasound excitation instead of conventional optical excitation, improving the tissue penetration depth of NIRF imaging in vivo. Q-SNAP consisted of the sonosensitizer NCBS, luminescent substrate DPAS, and GraB-sensitive quencher BBQ-650. In the presence of GraB, the quencher was released from Q-SNAP. Under ultrasound excitation, the sonosensitizer generated singlet oxygen to oxidize and produce a bright sonoafterglow. The sonoafterglow penetrated a tissue of 4 cm in thickness, overcoming the limited tissue

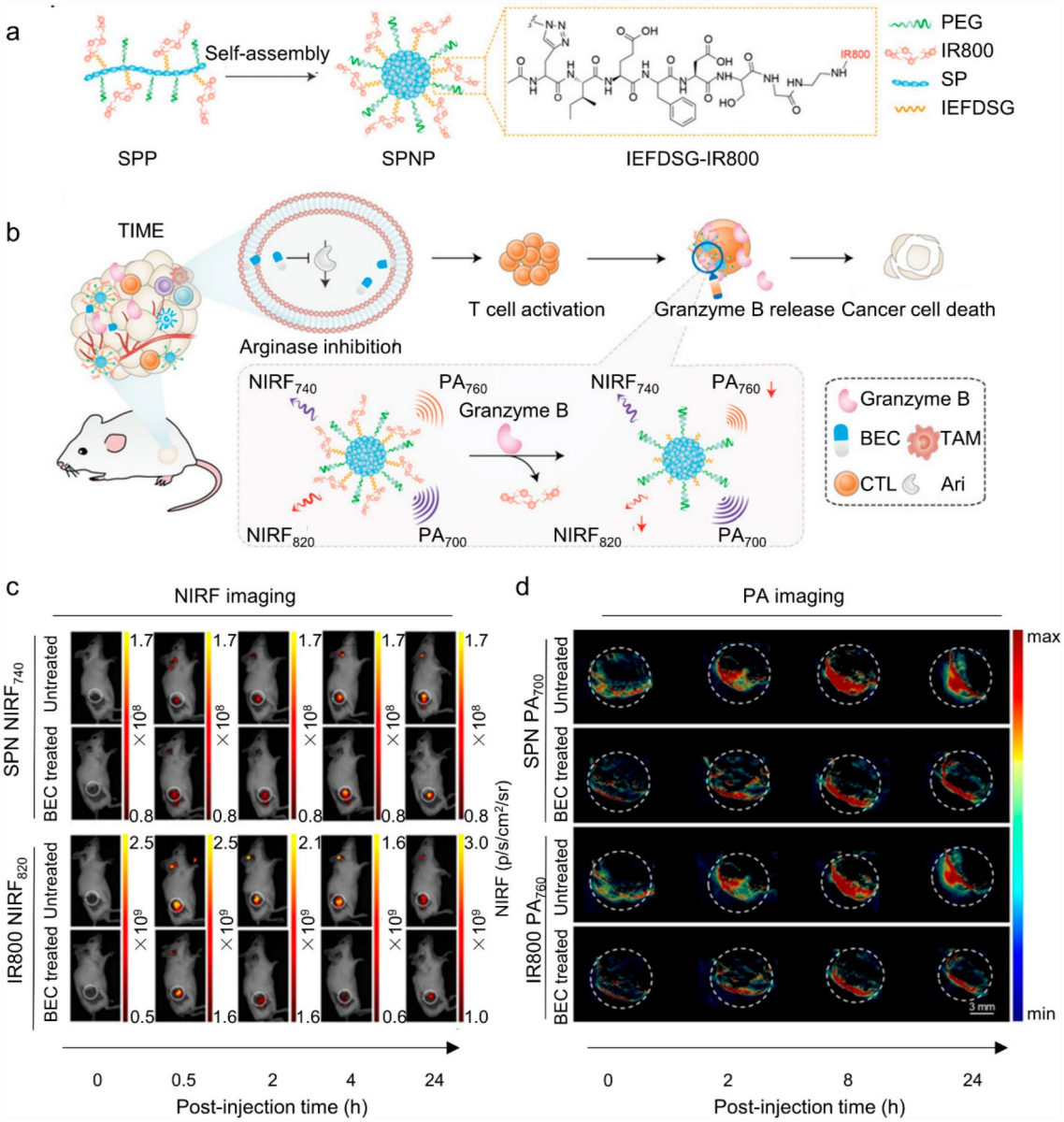

FIGURE 6 NIRF/photoacoustic imaging of CTL activation during cancer immunotherapy using an SPNP. (a) Preparation of the SPNP. (b) Mechanism for in vivo NIRF/photoacoustic imaging of activated CTLs. (c) NIRF imaging and (d) photoacoustic imaging of untreated and BEC-treated 4T1-tumor-bearing mice intravenously injected with the SPNP. Reproduced with permission [13]. Copyright © 2020 Wiley-VCH GmbH. CTL, cytotoxic T lymphocyte; NIRF, NIR fluorescent; SPNP, semiconducting polymer nanoprobe.

penetration depth of conventional fluorescence imaging. Q-SNAP can be repeatedly activated by ultrasound, and the detection limit of GraB was 2.1 nM, demonstrating high sensitivity of the imaging method. The authors used Q-SNAP to visualize liver-infiltrating T cells in mice with T-cell-mediated autoimmune hepatitis, providing a new imaging tool for early diagnosis of hepatitis. However, Q-SNAP has several shortcomings that limit its clinical application, including its complex composition, weak afterglow intensity, and customized imaging equipment. Xu et al. [58] prepared Cy5.5-CBT-NPs, which are a GraB-activated NIRF nanosensor formed by combining the fluorescent dye Cy5.5 and quencher TCEP through intermolecular hydrophobic interactions. In the presence of GraB, the Cy5.5 dye is released from Cy5.5-CBT-NPs, resulting in the generation of NIRF signals. Cy5.5-CBT-NPs facilitate sensitive and real-time monitoring of GraB-mediated CTL responses in vitro, and they have been used to evaluate the efficacy of S-(2-boronoethy1)-l-cysteine hydrochloride (a small-molecule immune-activating drug). However, the low stability and intratumoral administration of the nanosensor limit its clinical application. Nguyen et al. [53] designed an activatable GraB nanoreporter (αPDL1-GNRs) consisting of a fluorescent dye, quencher, short peptide, and immunotherapeutic drug (αPDL1). αPDL1-GNRs showed higher

sensitivity and selectivity compared with conventional imaging probes. Additionally, they enabled monitoring of the immunotherapy response in various tumor-bearing mouse models, providing a tool to evaluate immunotherapy efficacy.

3 | OPPORTUNITIES AND CHALLENGES FOR THE APPLICATION OF OPTICAL IMAGING TO IN VIVO VISUALIZATION OF ACT IMMUNE CELLS

Various optical imaging probes have been used for in vivo visualization of ACT immune cells, providing multi-scale and multi-level visual information to evaluate the molecular mechanism, efficacy, and side effects of ACT [59, 60]. The fusion of optical and clinical imaging, such as MRI, PET, and CT, has the potential to fully elucidate the in vivo fates of ACT immune cells and promote the development of ACT. Significant advances have been made in the application of ACT in the treatment of hematological tumors, but the application of such immunotherapy in the treatment of solid tumors remains in its early stage [61, 62]. This provides an excellent opportunity to develop optical imaging probes to promote the development of ACT. The following are strategies to promote the application of optical imaging probes to in vivo visualization of ACT immune cells in clinical settings: (i) improving the luminescence-generating performance of optical imaging probes by preparing fluorescent probes with high fluorescence quantum yields, long emission wavelengths, and high water solubility to enhance the sensitivity of in vivo visualization ACT immune cells; (ii) developing efficient strategies to label ACT immune cells as improved alternatives to existing direct and indirect labeling methods to improve the specificity of in vivo visualization of ACT immune cells [63]; (iii) reducing the in vivo toxicity of optical imaging probes by developing metabolizable optical imaging probes with low toxicity [64]; and (iv) developing optical imaging nanoprobes that integrate multiple imaging modalities, particularly PET and optical imaging [34].

AUTHOR CONTRIBUTIONS

Qingshuang Li, Dehong Hu, and Duyang Gao contributed to drafting of the manuscript and collation and analysis of the literature. Can Zhang and Zonghai Sheng contributed to the conception and critical revision of the manuscript and approved the final version of the submitted manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analyzed in this review.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Not applicable.

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