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Photothermal nanomaterials for theranostics of atherosclerosis and thrombosis

Karla X. Vazquez-Prada [a,b], Shehzahdi S. Moonshi [a], Zhi Ping Xu [b], Hang Thu Ta [a,b,c,*]

[a] Queensland Micro- and Nanotechnology Centre, Griffith University, Nathan, Queensland 4111, Australia
[b] Australian Institute for Bioengineering and Nanotechnology, the University of Queensland, St Lucia, Queensland 4072, Australia
[c] School of Environment and Science, Griffith University, Nathan, Queensland 4111, Australia

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ABSTRACT

Nonradiative therapies focusing on converting energy from light into heat (photothermal therapy, PTT) have been widely studied for the treatment of cancers. In the last years, interests in the potential therapeutic efficiency of PTT in cardiovascular diseases have grown quickly. Nonetheless, research in this field is still limited and requires further attention. One of the advantages of nanocarriers used as photothermal agents is the possibility to integrate multimodal imaging and therapeutic functions as a solution to address the current limitations in the clinic. In this review, we first explain the mechanism of nanoparticle-mediated photothermal therapy and summarize the advances in the development of inorganic, organic, and hybrid nano photothermal transduction agents (PTAs). Then we discuss the toxicity, challenges and limitations encountered in the development of phototherapy for cardiovascular diseases. The review concludes with highlighting possible solutions for improving PTT in this specific field.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and contributes enormously to the global morbidity [1,2]. Atherosclerosis in particular is responsible for 30 % of deaths annually and its burden is predicted to rise in the next few years [1–3]. Atherosclerosis is an inflammatory, multifactorial, and progressive disease characterised by deposition of lipids within the artery wall [4–6]. Atherosclerosis initiates when lipoproteins infiltrate and accumulate in the intima, activating the endothelium. The activated endothelium promotes the production of chemokines and growth factors that encourage cell migration, proliferation, and recruitment of circulating immune cells (*i.e.* leukocytes, monocytes, etc.) [7]. This inflammatory response generates loss of the morpho-functional integrity of the endothelium, also known as endothelial dysfunction [8]. Activated endothelial cells express adhesion molecules, which cause white blood cells adhesion on the vascular surface [9]. Monocytes that have entered the intima differentiate into macrophages expressing receptors that contribute to internalization of apoptotic cell fragments and oxidized-low density lipoprotein particles. Macrophages with lipidic depositions contribute to foam cell formation and trigger the production of inflammatory cytokines, proteases, and cytotoxic radical molecules, which damage the extracellular matrix [10]. This events altogether compromise the stability of the atherosclerotic plaque and increase its vulnerability and the eventual risk of rupture.

Atherosclerosis alone is rarely fatal and remains asymptomatic when stable, it is the main trigger of other life-threatening diseases [1,3,11,12]. For example, if the plaque becomes large enough to obstruct the lumen or ruptures, it might lead to platelet aggregation, blood coagulation, thrombus formation (thrombosis), myocardial infarction, stroke, or peripheral artery disease [13,14]. Thrombosis occurs when coagulation of the blood forms clots within blood vessels [15]. Thrombosis can be divided into arterial thrombosis (AT) and venous thrombosis (VT). The first one takes place in the arteries and generally involves rupture of an atherosclerotic plaque. VT on the other hand refers to a hypercoagulable state, vascular wall injury and circulatory stasis [16].

An early diagnosis and rapid treatment of thrombosis are crucial for its effective treatment and one of the biggest challenges to decrease

Honorary Associate Professor, Australian Institute for Bioengineering and Nanotechnology, University of Queensland, St Lucia, Brisbane QLD 4067, AustraliaOffice: +61 (7) 3735 5384Website: https://hangta.group/https://experts.griffith.edu.au/27034-hang-ta

* Corresponding author at: School of Environment and Science and Queensland Micro- and Nanotechnology, Griffith University, Nathan Campus, Brisbane, QLD 4111, Australia.

E-mail address: h.ta@griffith.edu.au (H.T. Ta).

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morbidity, mortality and rate of recurrence [17–20]. Current treatment of thrombosis, including anticoagulants, antiplatelet agents, thrombolytic drugs, and catheter-based techniques are either invasive or present fatal side effects such as haemorrhages [21,22].

Strategies like the development of new treatments such as photothermal therapy (PTT) for ablation of thrombi are emerging to reduce undesired side effects [23]. PTT is a treatment approach where hyperthermia (increase in temperature) in a specific region is achieved by converting energy from photons to thermal energy [24]. Whilst research in nanomedicine is producing novel tools for diagnosing and treating CVD [25,26], advances from the nanomedicine field to tackle CVDs are still relatively limited [27]. Since 2005, only about 3.65 % of nanomedicine publications and 0.38 % of the entire nano-industry have been dedicated to the research of nanocarriers for drug delivery, nano-contrast agents for imaging, and nanomaterials for PTT of atherosclerosis [28]. Moreover, the amount of research in nanomedicine for CVDs constitutes only 4.82 % [29]. Novel nanomaterials that combine imaging and therapeutic functions have the potential to improve the efficacy and accuracy of diagnosis and provide rapid treatment alternatives. Nanomaterials with both diagnostic and therapeutic capacity are termed nanotheranostics. Nanotheranostics represent one of the latest frontiers in precision medicine as they can provide insights regarding the biodistribution, release, and efficacy of treatment *in vivo* in real-time [30].

Several reviews have been published to discuss nanomaterials used as photothermal agents [26,31–34], photothermal therapy for cancer [35,36], and the challenges and emerging approaches such as synergistic therapy, nanotheranostics or image-guided PTT [37–39]. Importantly, there is only one review focusing on PTT for atheroregression, which aims to anticipate and describe nanoagents that could be potentially used for clinical application in interventional cardiology [40]. To the best of our knowledge, there is still not a review focusing on the work done so far for PTT of CVDs. This review presents, for the first time, the advances of nanomaterials used as theranostics for atherosclerosis and thrombosis, focusing on PTT as the therapeutic approach to treat CVDs.

1.1. Photothermal therapy

PTT relies on photothermal transduction agents (PTAs), also known as photosensitizers, and their photothermal effect (PTE). PTE refers to the phenomena caused by the conversion of light energy into thermal energy (heat) [41]. The conversion leads to an increase of the temperature in the surrounding environment, which triggers the death of cells and ablation of masses and clumps such as tumours and thrombi [42,43]. The use of an external laser with the adjustable powder density is one of the advantages of PTT as it allows precise targeting and decreases the damage and adverse effects to the healthy tissues surrounding the disease area [36].

Enormous effort has been made through the years to mitigate the intrinsic limitations of the classical molecular photosensitizers. Some of the challenges of first-generation photosensitizers tested in the clinic included their poor treatment efficiency, instability in water, their low selectivity to the disease site, and short half-life [44]. Second-generation photosensitizers aimed to increase their water stability by introducing hydrophylic substituents to their structure [45]. However, this addition increased its renal clearance and therefore decreased the bioavailability of the photosensitizer.

Clinical studies using first- and second- generation photosensitizers highlight the need for improved pharmacokinetic profiles, physicochemical properties, and specific targeting to enhance accumulation at the disease site and better therapeutic outcomes [46]. Third-generation photosensitizers are hybrid photosensitizers with other chemical moieties such as proteins, liposomes, or nanoparticles, developed to enhance biodistribution, bioaccumulation, cell uptake and accumulation. Macromolecules such as proteins and nucleic acids are usually unable to internalize cells. Nonetheless, when they are formulated in nanoparticles, internalization occurs via endocytic pathways [47]. Nanoparticles increase the half-life and the retention time of the photosensitizer within the body than small molecule fluorophores, allowing for improved imaging and therapy over a longer period, and improving photostability [48–50].

Nanophotosensitizers have gained interest due to their enhanced permeability, active targeting, and retention efficacy [51]. Nanomaterial-mediated photothermal therapy combines targeting biomolecules for high specificity and suppression of adverse effects [52,53]. Nanoparticles used as PTAs have shown higher PTE than molecular PTAs [36]. In addition, nano-PTAs can integrate multiple imaging modalities and therapeutic functions for advanced applications [36]. The general process of nanoparticle-mediated PTE is shown in Fig. 4 [52]. Briefly, nanoparticles accumulate in the target (*i.e.*, atherosclerotic plaque **(**Fig. 4**B)** or thrombus **(**Fig. 4**C)** due to active or passive targeting. The temperature rise produced by the adsorbed laser energy reduces the atherosclerotic plaque by ablation of macrophages or loosens the blood clot by destroying interactions between fibrins and induces apoptosis of cells in the clot [54].

1.2. Surface plasmon resonance and nanomaterials

Materials that can achieve exceptional optical properties by light-matter interactions are called plasmonics [55]. Plasmonics exploit their surface plasmon resonance (SPR) effects to transform light into other forms of energy such as heat or acoustics [36]. SPR is the generation of a resonance effect due to the interaction of conduction electrons (plasmons) from transducers when exposed to a specific incident wavelength, causing an enhancement in light scattering and absorption of energy [56]. The incident light penetrates the material and polarizes the conduction of electrons, causing different effects such as a local increase in the temperature [57] and thermoelastic expansion [58]. The former causes hyperthermia and enables a promising non-invasive PTT, whilst the later leads to the generation of ultrasonic waves that can be transduced into images for diagnosis (PAI).

The ideal design and synthesis of an effective photothermal nanoagent strongly rely on its SPR. This optical phenomenon is caused by light waves trapped within conductive nanoparticles with a wavelength shorter than that of light [59]. SPR is the resonant collective oscillation of valence electrons from the nanomaterials [60]. This collective oscillation promotes light–matter interactions and generates stimulation of the phonon mode. The SPR-induced electron and phonon modes stimulated by light momentarily relax and cause thermal lattice expansion (extensional mode). The stimulation of metastable atom/ion displacement pushes the limits of plasmonics and change the material's properties [61]. For example, when metallic nanoparticles with high SPR absorb light, the electrons in the conduction band are heated up to a very high electronic temperature and then thermalized to reach a new equilibrium via electron–electron scattering [62]. The energy then flows from electrons to the ion lattice through electron–phonon coupling. Lastly, the energy is dissipated into the environment through heat transfer and diffusion [62].

The scattering and absorption efficacy of the nanoparticle depend on the properties (material, size, shape) and the laser wavelength used to irradiate. SPR effects can be enhanced based on the coating material, surface modification, particle interaction, and surface charge [63]. The morphology of the nanomaterial will affect its dielectric environment and the manner in which the energy is diffused. Tuning the shape of the nanoparticle might be one approach for shifting the absorbance peak of the material [64]. Near-infrared region (NIR) is optimal for biomedical applications because of the high extinction coefficient at wavelengths ~750 nm −1000 nm and the poor absorption of biological materials and tissues at these frequencies, suggesting it might be less invasive than visible light laser [65].

Different methods have been developed to produce nanoparticles with a variety of geometries such as cubes, rods, shells, triangles and

stars [66]. Elongating a spherical nanoparticle into a rod-like shape or nanostars tends to shift the SPR into the NIR because asymmetrical shapes have lower energy compared to the spheric ones [57,66,67]. Asymmetrical nanoparticles can achieve higher temperatures due to the larger absorption cross-section than symmetric ones with the same volume [68]. Fig. 5 summarizes the classification of the transduction nanoagents that have been used for theranostics of thrombosis and atherosclerosis using PTT.

The ideal theranostic nanomaterial for CVDs needs to integrate the functions of targeting, imaging, and therapeutics in one particle. Materials with the ability to be tuned and adapted for loading therapeutic, imaging molecules and/or targeting ligands are desired for cardiovascular theranosis [69]. In addition, the development of nanoparticles from conventional materials that have been previously used as FDA-approved medical devices for CVDs rather than a brand-new material is also preferred. The use of conventional materials not only reduce toxicity concerns and adverse effects but will also aid with the regulatory process and speed up its translation to the clinic. Therefore, the most used materials to date for cardiovascular nanomedicine are carbon-based, polymeric, lipid/protein-based or metallic, particularly gold and iron oxides [70].

Table 1 summarizes the nanotheranostics that have been studied for CVDs, in particular atherosclerosis and thrombosis. Some studies have only performed *in vitro* tests, while others have been able to demonstrate the PTA's efficacy *in vivo*. The table shows some of the relevant parameters to illustrate the differences and similarities among PTAs developed for nanotheranostics of CVD using PTT. Unfortunately, some parameters related to the PTA and experiment settings have not been reported in some manuscripts (*e.g.* laser beam size, PTA concentration, and size) and therefore, not shown in the table. This hinders our ability to compare efficacy and potential side effects across the reported PTAs.

2. Photothermal nanomaterials for theranostics of CVDs

2.1. Inorganic transducers

2.1.1. Metallic-based nanotheranostics

Relatively few inorganic materials are known to have strong SPR [57]. Research on photothermal ablation has been focused on gold nanoparticles, although silver, copper and aluminum are also elements that have SPR at the nanoscale and are gaining interests for photothermal therapy [57,63,81,82].

Most investigations on gold-based nanomaterials for PTT of CVDs have been done in atherosclerosis. PTT of inflammatory macrophages has great potential in treating atherosclerosis due to the key role of inflammation and macrophages in the pathogenesis of the disease [83]. Gold nanorods (AuNRs) and gold nanoparticles (AuNPs) have been developed for this purpose [84–86].

AuNRs have been tested as theranostics for *in vitro* and *in vivo* imaging and PTT of macrophages using a femoral artery restenosis model in Apo E-/- mice [84]. On the other hand, AuNRs are able to cause hyperthermia in the macrophages under laser irradiation and induce ablation via hyperthermia of macrophages both *in vivo* and *in vitro*. Uptake of the AuNRs was demonstrated by *in vitro* micro-CT imaging. Nonetheless, CT images of Apo E/- mice with femoral artery restenosis did not show significantly enhanced intensity after intravenous injection of the AuNRs. Thus, further studies are needed to confirm the efficacy of AuNRs as a diagnostic agent.

The plasmonic properties of AuNRs have also shown to enhance PAI of macrophages. Silica-coated gold nanorods (SiO_2AuNR) [86] were able to image atherosclerotic plaques and monitor temperature changes via combined intravascular ultrasound and photoacoustic imaging (IVUS/IVPA). In this study, an atherosclerotic human right coronary artery section from a 71-year-old male patient was employed for *ex vivo* imaging. The artery was injected with SiO_2AuNR used for imaging photothermal heating. Under NIR laser, an increase in the photoacoustic signal for the section containing SiO_2AuNR indicated hyperthermia. It is important to note that the results acquired from this model design might not translate into the clinic as it does not mimic the physiological environment nor takes into consideration the ability of the nanoparticles to accumulate in the plaques *in vivo*. An adequate control for the *in vivo* imaging and monitoring photothermal heating to evaluate the targeting efficiency of the nanosystem to atherosclerotic plaques and its toxicity in the body is required before moving forward to clinical trials. Although these results serve as proof of concept for inducing, detecting and monitoring PTT in atherosclerotic plaques, it is necessary to further validate the therapeutic efficacy of IVUS/IVPA-monitored PTT for atherosclerotic plaques *in vitro* and *in vivo*.

Hollow-type gold nanoparticles (AuNPs) have also been explored for PTT and imaging of macrophages in atherosclerosis [85]. Upon NIR laser irradiation, macrophages labelled with AuNPs were selectively damaged. FACS analysis revealed that the ablation of the cells was caused by late apoptosis-related cell death or secondary necrosis due to the photothermal effect of AuNPs. Importantly, the change in temperature increased with increasing the laser power used. Although this study generated insights towards the efficacy of the nanoparticles as a potential nanotheranostic agent, *in vivo* studies with an appropriate atherosclerosis model are required to identify potential caveats and challenges for clinical translation.

Ma et al. [87] reported a nanorose-like shaped system with a strong NIR peak based on gold-coated iron oxide nanoparticles (AuIONPs) for theranostics of atherosclerosis. IONPs have been employed in numerous studies for imaging of diseases [23,88–101]. In this study, IONPs were incorporated into the nanosystem to provide a multimodal imaging ability, as IONPs have strong magnetic resonance imaging (MRI) contrast [83]. The AuIONPs were also coated with dextran, a molecule shown to bind effectively to macrophages [102]. Macrophages showed high uptake of the nanoparticles. Laser photothermolysis of macrophages *in vitro* was observed. Hyperspectral microscopy showed high contrast due to the SPR of gold in the nanosystem both in cell culture and in an *in vivo* rabbit model of atherosclerosis. While *in vivo* imaging of atherosclerotic rabbits showed that the AuIONPs could effectively accumulate in the plaques, no *in vivo* PTT assays were performed. Nonetheless, these results provide promising insights and encourage further work in developing theranostic nanosystems combining properties from diverse materials. AuIONPs was also developed by Fithri et al. and had a spiky shape with size around 100 nm [71]. The team employed this AuIONPs for theranostics of thrombosis. The NPs were labelled with a single-chain antibody that specifically targeted activated platelets on thrombus. Detection of the clots was achieved by triple imaging modalities including MRI, PAI and fluorescence imaging. Upon stimulated by 3 cycles of 808 nm laser light at 1.5 W/cm^2 for 3 min, approximately half of the clot was lysed. Although a complete thrombolysis was not observed in this study, opening of blood vessel lumen was achieved, which would be highly beneficial for emergency treatment of blood clotting events.

Silver (Ag) is a metallic transducer that has demonstrated strong NIR absorbance and capability to coat IONPs [72]. Even though gold is the most studied metal for PTT, some studies show that silver is a metal with higher efficiency of plasmon excitation in the visible spectrum, in comparison to gold [103,104]. *In vitro* MRI images of macrophages and thrombi with silver-coated iron oxide nanoparticles functionalized with pprox.lic acid (Ag-IO-PAA) demonstrated significant signal loss in T_2-weighted images. *In vitro* thrombi PTT assay showed a dose dependent increase in the temperature of the clots when exposed to the laser. Moreover, a decrease in thrombi mass of approximately 50 % was observed at the highest concentration of Ag-IO-PAA. This study provided evidence of silver being an excellent PTA at the nanoscale but lacked evidence of its activity *in vivo* and its ability to serve as contrast agents for other imaging modalities. Therefore, the same group performed a follow-up study assessing its PTT ability *in vivo* and examining diagnosis imaging with other modalities such as PAI. Here, the authors

Table 1
Photothermal nanomaterials for theranostics of CVDs.

Classification	Nanosystem (shape, size)	Photo-thermal conversion efficiency	Diagnostic element and modality used	Thera-peutic agent	CVD	Laser settings*	In vivo dose	Animal model and/or Therapeutic outcome#	Year and ref
Metallic	AuNRs (nanorods, ~60 nm)	–	CT (Au)	Au	Athero-sclerosis	808 nm, 2 W.cm^{-2}, 10 min	0.4 μmol Au/g of body weight	Femoral artery restenosis mouse model. Mice treated with AuNRs showed a significant increase in temperature when compared to control.	2021 [84]
	AuNPs (hollow-type spheres, ~60 nm)	–	Dark field microscopy (Au)	Au	Athero-sclerosis	808 nm, 0–5.56 W. cm^{-2}, 3 min (*in vitro*)	–	In vitro study: Treatment with the nanoparticles induced apoptosis and necrosis on RAW 264.7.	2008 [85]
	SiO_2AuNRs (nanorods)	–	Ultrasound and PAI (Au)	Au	Athero-sclerosis	808 nm, 60–200 mW,45 s (*in vitro*)	–	In vitro study: Linear relationship between photoacoustic pressure generation and change in temperature of J774. AI	2013 [86]
	AuIONPs (nanoclusters, ~30 nm)	–	MRI (Fe) Hypers-pectral microscopy (Au)	Au	Athero-sclerosis	755 nm, 18 J.cm^{-2}, 50 ns pulse (*in vitro*)	–	In vitro study: Treatment with AuIONPs resulted in a temperature increase of 0.7 Celsius and apoptosis of primary macrophages isolated from C57/ BC6 mice.	2009 [87]
	AuIONPs (nanoclusters, ~ 100 nm)	37.47 %	MRI (Fe) Fluor-escence (Cy5) PAI (Au)	Au	Throm-bosis	808 nm, 1.5 W.cm^{-2}, 3 min on 5 min off, 3 cycles	6.5 mg NP /kg of body weight (328 μg Fe/kg & 3.08 mg Au/kg)	$AlCl_3$- induced thrombosis mouse model. An increase in temperature of 19.5 Celsius and a thrombolysis 45 % greater than that of the control was shown by the AuIONPs treated group.	2023 [71]
	Ag@IO-PAA (nanoclusters, ~120 nm)	–	MRI (Fe)	Ag	Throm-bosis	808 nm, 1.59 W.cm^{-2}, 1–3 min (*in vitro*)	–	In vitro study: 33 % of ROS were scavenged in the group treated with Ag@IO-PAA. Moreover, the thrombolysis obtained from treated groups was ~50 % higher than that of the PBS group.	2021 [72]
	AgIONPs (nanoclusters, ~140 nm)	23 %	MRI (Fe) Fluor-escence (Cy5) PAI (Ag)	Ag	Throm-bosis	808 nm, 1 W.cm^{-2}, 2.5 min on, 2.5 min off, 3 cycles	4 mg/kg of body weight	$AlCl_3$- induced thrombosis mouse model. Temperature increase (~15 Celsius) and thrombolysis (~80 %) were significantly higher in the groups treated with AgIONPs + laser when compared to other controls.	2023 [15]
	Fe_3S_4NPs (spheres, ~18 nm)	–	MRI (Fe)	Fe	Throm-bosis	808 nm 0.33 W.cm^{-2}, 5 min (*in vitro*)	12 mg/kg of body weight	In vitro study: Fe_3S_4NPs exhibited a much higher temperature increase when exposed to NIR laser and AMF *in vitro* than that of those nanoparticles irradiated with either AMF or NIR alone. Nonetheless, when using a Deep Vein Thrombosis mouse model, the laser (setting not reported) did not have enough depth to reach lesions and burns were caused. Therefore, the authors only tested AMF's ability to lyse thrombus *in vivo*.	2019 [73]
	CuS-TRV1 (spheres, ~13 nm)	–	Ultrasound PAI (Cu)	Cu	Athero-sclerosis	980 nm 5 W.cm^{-2}, 30 cycles 30 s on, 30 s off, twice weekly, 12 weeks	10 mg/kg of body weight	Plaque bearing ApoE-/- mice were used. A reduction of 72.3 % in aortic lesions was seen in mice treated with the nanoparticle when compared to the control.	2014 [74]
Carbon-based	SWCN (nanotubes)	–	Fluor-escence (Cy5.5)	C	Athero-sclerosis	808 nm, 5 W.cm^{-2}, 5 min	0.6 nmol/ mouse	Carotid ligation of FVB mice was performed in this study. There was a significant photothermal ablation of vascular macrophages in ligated carotids with SWNTs plus laser light exposure when compared to control group.	2012 [75]

(*continued on next page*)

Table 1 (*continued*)

Classification	Nanosystem (shape, size)	Photo-thermal conversion efficiency	Diagnostic element and modality used	Thera-peutic agent	CVD	Laser settings*	In vivo dose	Animal model and/or Therapeutic outcome#	Year and ref
Organic	GCS-PPY-H (spheres, ~150 nm)	14.7 %	Fluor-escence (Cy5)	Polypyrrole Heparin	Throm-bosis	808 nm, 2.45 $W.cm^{-2}$, 5 min on, 3 min off, 4 cycles	–	$FeCl_3$- induced thrombosis mouse model. Around 5 Celsius and 20 % more thrombolysis in the GCS-PPY-H treated group when compared to control.	2021 [76]
	DS-Ce6 (spheres, ~50 nm)	–	Fluor-escence (Ce6)	Ce6	Athero-sclerosis	670 nm, 1 $W.cm^{-2}$, 150 s	2 mg of Ce6/kg of body weight	Atherogenic mice were used for this study. Macrophage areas decreased around 57.6 % more in treated group. Moreover, plaque areas in treated mice were 29.2 % lower in this group than those of the control.	2021 [77]
Hybrid	CS-CNCS@Ce6/DS (spheres, ~200 nm)	–	Fluor-escence (Ce6)	Ce6	Athero-sclerosis	PTT: 808 nm, 1 $W.cm^{-2}$, 10 min PDT: 633 nm, 80 $mW.cm^{-2}$ 10 min	–	Partial ligation of left carotid artery and fat-diet fed mice were used. The highest atherosclerotic plaque regression was found in the groups treated with CS-CNCS@Ce6/DS, 633 nm laser (PDT) followed by 808 nm laser (PTT) exposure.	2021 [78]
	ALA:AuNPs (spheres, ~5–40 nm)	–	Fluor-escence (PPIX)	Au	Athero-sclerosis	–	57.7 mg/kg of body weight	The trace of porphyrin in blood and feces of NZ rabbits serve as preliminary evidence that ALA:AuNPs accumulate in plaques and could potentially be tracked with fluorescence of PPIX in tissues.	2015 [79]
	Fu-Uk/ICG@Si-AuNRs (nanorods, ~10 nm)	–	Fluor-escence (ICG) CT and X-ray (Au)	Au Uro-kinase Fuc-oidan	Throm-bosis	808 nm, 2 $W.cm^{-2}$, 5 min	100 U of Uk/ g of body weight	ICR mouse model of mesenteric thrombosis. Greatest increase of thrombolysis was shown by Fu-Uk/ICG@Si-AuNRs, with a 1.7-fold higher than the control.	2021 [80]

* In vivo laser settings unless stated otherwise.
\# In vivo therapeutic outcomes unless stated otherwise.

developed a spiky nanoparticle with strong absorbance in the NIR (AgIONPs) [15]. The AgIONPs were also labelled with Cy5 and were designed to target activated platelets in the thrombus. Binding assays showed a highly specific binding to human thrombus and activated platelets. Fluorescence imaging and PAI studies showed that AgIONPs could be used as a multimodal diagnostic agent for thrombosis. Laser-enhanced thrombolysis *in vitro* and *in vivo* in an $AlCl_3$ thrombosis model resulted in an increased effect of thrombolysis when exposed to 808 nm laser (Fig. 1**A, B**). Photothermal thrombolysis *in vivo* showed an increase in the temperature in mice treated with AgIONPs (Fig. 1**A**). Blood flow was significantly restored in the targeted groups but not in the non-targeted one (Fig. 1**C**). Importantly, hemocompatibility assays on red blood cells, viability assays on CHO and endothelial cells, and histology analysis suggested no apparent toxic effects of AgIONPs, suggesting this nanosystem could be a potential non-invasive, effective, and safe theranostic agent for thrombosis.

Bare iron nanoparticles have been widely explored in nanomedicine for specific-target heating purposes due to its excellent magnetic field hyperthermia and PTE [33]. Magnetic iron sulfide nanoparticles (Fe_3S_4NPs) have shown to be a promising nanotheranostic agent for combined magnetocaloric and photothermal therapy of thrombosis [73]. *In vitro* magnetocaloric conversion performance of Fe_3S_4NPs showed an increase in temperature of 12.8 °C upon external alternating magnetic field (AMF) stimulation. Photothermal conversion performance *in vitro* upon laser exposure showed higher increase in temperature than with AMF (30 °C). Importantly, exposure of the nanoparticles to combined AMF and NIR resulted in an increase in temperature of 37.1 °C. These *in vitro* data gave insight of a possible synergistic relation when using both triggers. The thermal conversion effect of Fe_3S_4NPs under the co-stimulation of NIR and AMF was tested *in vitro* in a thrombus model. As expected, the thrombi were partially lysed under the stimulation of NIR or AMF due to hyperthermia caused by one stimulation but completely lysed when co-stimulated by NIR and AMF. Although interesting, the lack of reporting of specific quantities (*i.e.*, percentage ablation) hinders our ability to assess whether a true synergistic effect arose from combining NIR and AMF. Instead, the temperature increases described above would suggest antagonism as a negative deviation from additivity of effects (*i.e.*, the combined effect is lower than the sum of the individual effects) was observed. Antagonism could suggest that the physical underpinnings of the temperature increases caused by NIR and AMF are shared. *In vivo* T_2-weighted MR imaging guided magnetic hyperthermia of thrombi was performed in a deep vein thrombosis model using black C57BL6 mice. Under AMF excitation, the MRI signal intensity showed a correlation with the nanoparticle concentration, suggesting magnetocaloric therapy can be monitored via MRI. Importantly, the heat produced from laser exposure with NIR *in vivo* was shown to burn the hair of the animals. Thus, optimization of PTT, aiming at reducing surrounding tissue harm, is necessary.

Some possible solutions to prevent skin burns while doing PTT include reducing the nanoparticle concentration, decreasing the time of exposure or intensity of the laser, or irradiating with shorter time for several cycles, allowing cooling periods between them. For instance, in the above study the temperature increased by 37 °C using 0.5 mg/mL whole NPs, which translated to more than 50 °C in the area treated, enough for causing burns in surrounding tissue [107]. Other research papers have shown that hyperthermia induced thrombolysis with less than 20 °C change in temperature [72]. Future studies need to explore

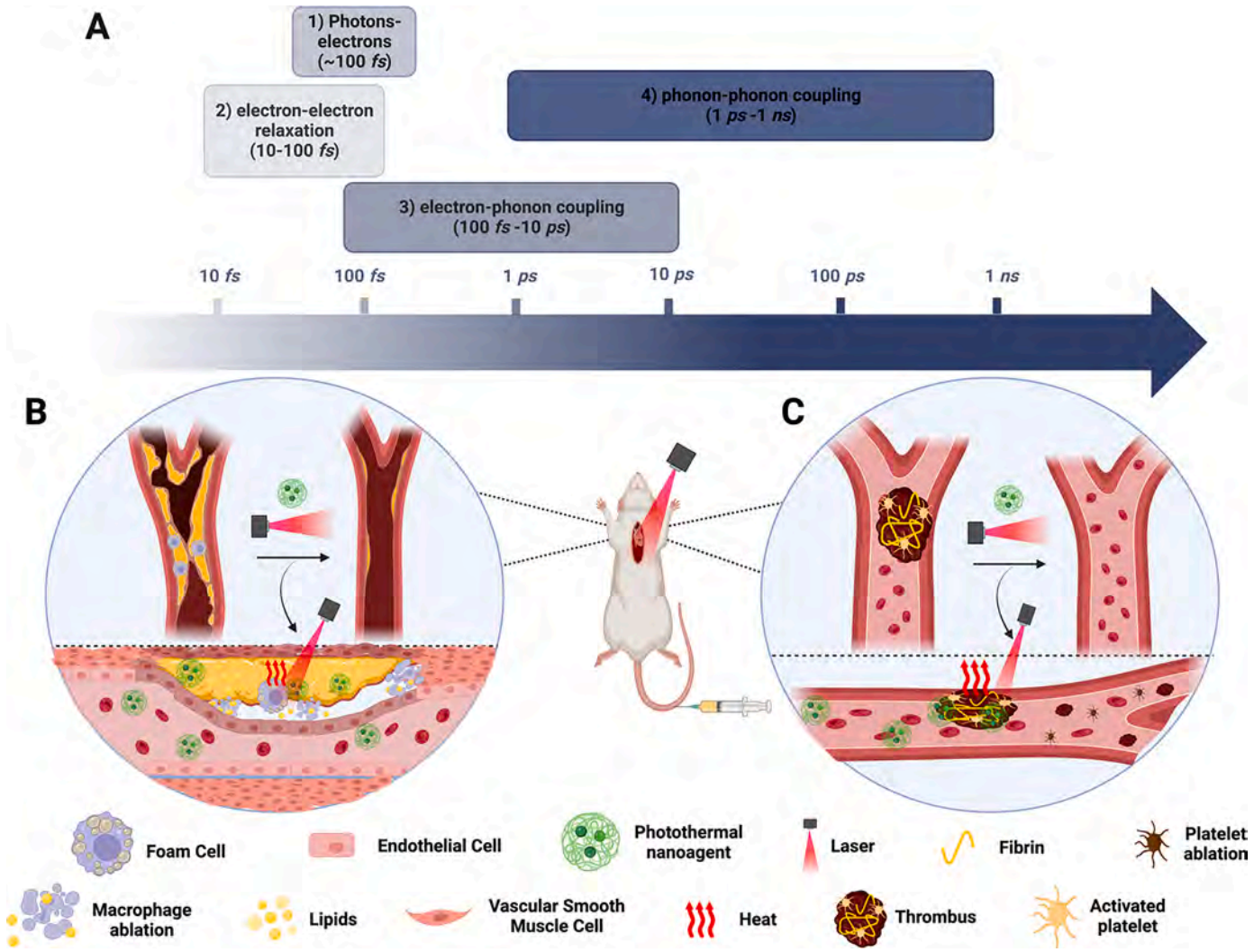

Fig. 1. Steps (A) and mechanisms of nanoparticle-mediated photothermal therapy for atherosclerosis (B) and thrombosis (C). First, the nanoparticles bind to either the atherosclerotic plaque or the thrombus. Once the nanoparticle is accumulated in the disease site, local hyperthermia is triggered by exposure to laser light. A1) On a time scale of 100 *fs,* free electrons absorb energy of photons, A2) a state of the equilibrium distribution is achieved by electron-electron relaxation, consequently A3) electron-phonon coupling effect causes the nanoparticle to increase its temperature, and finally A4) energy exchange between the nanoparticles and their surrounding medium causes the temperature to rise due to phonon-phonon coupling (information retrieved from [105]). In the case of atherosclerosis (B), activated macrophages in the form of foam cells are ablated due to the photothermal conversion capability of the nanoparticle. Interestingly, it has been shown that photothermal ablation of macrophages can also reduce pro-inflammatory cytokine secretion and alleviate the proliferation and migration of cells involved in the progression of atherosclerosis, which stabilizes and decreases the size of the atherosclerotic plaque [78]. C) Shows the photothermal mechanism for treatment of thrombosis. The local heat generated by the nanophotosensitizer not only causes hyperthermia, but also produces mechanical energy from water vapor that leads to bubble generation at the nanoscale [106]. These energies not only disrupt fibrin strands and dehydrate proteins involved in the thrombus, but also alter the membrane fluidity of cells, facilitating thrombolysis. Figure created with BioRender.

the possibility of using lower concentrations (*i.e.* 0.1–0.5 mg/mL) to produce an increase in temperature that allows a safe treatment.

Copper has excellent photothermal coupling effects, which makes it a promising candidate for PTT [108]. Lipidic accumulation in vascular smooth muscle cells (VSMCs) leads to the formation of foam cells, a crucial step in atherosclerotic progression [109]. Inducing autophagy in oxidized low-density lipoprotein (oxLDL)-treated VSMCs has been found to protect against foam cell formation. Transient receptor potential vanilloid subfamily 1 (TRPV1) has been shown to reduce foam cell formation upon activation [110]. Copper sulfide nanoparticles were conjugated to antibodies targeting TRPV1 (CuS-TRPV1) to test the efficacy to act as a photothermal switch for TRPV1 signaling in VSMCs and as a contrast agent for PAI [74]. Exposure to NIR laser caused hyperthermia in VSMCs incubated with CuS-TRPV1. *In vitro* photothermal induction of autophagy was shown to inhibit oxLDL-induced VSMC foam cell formation. *In vivo* PAI in plaque-bearing ApoE−/− mice showed accumulation of CuS-TRPV1 in the region of interest increased over time. CuS-TRPV1 + laser treatment limited atherosclerotic lesion progression in ApoE−/− mice compared to controls. *Ex vivo* results corroborated reduction in aortic lesion areas compared with the control group.

2.2. Carbon-based materials

Carbon-based materials are known to have exceptional optical performance in the NIR and are excellent converters for induction of hyperthermia [111]. Single-walled carbon nanotubes (SWCN) possess unique physicochemical properties and therefore are of particular interest in bioimaging, drug delivery, and PTT [75]. However, there is only one study using SWCN as the PTA for PTT of CVDs. Kosuge et al. developed Cy5.5-SWCN to investigate macrophage imaging and PTT of macrophages in a murine model of vascular inflammation. When

exposed to a NIR laser, macrophages with SWNTs showed a 93±3 % reduction in viability. Fluorescence imaging *in vivo* and ex vivo exhibited a significant increase in fluorescence of treated mice (Fig. 2A). NIR laser exposure of freshly excised arteries treated with SWNTs showed a temperature increase and immunohistochemistry data corroborated induced apoptosis in the neointima and adventitia of arteries due to the PTT (Fig. 2B). While SWNTs were able to image and ablate vascular macrophages, further development and evaluation of an *in vivo* vascular PTT system need to be done for this nanosystem. Currently, it is hard to predict the effects of PTT with SWCTs, and therefore evaluate whether they will be useful in developing safe and non-invasive procedures.

2.3. Organic plasmonics

Inorganic nanomaterials are usually not biodegradable [112]. Consequently, a variety of organic photothermal agents has emerged aiming to replace their inorganic counterparts. There are only three studies reporting organic plasmonics as theranostics using PTT for CVDs [76–78] . These studies are based on either polypyrrole (Ppy) or chlorin e6 (Ce6).

Ppy is one of the most studied organic conductors due to its good environmental stability and easy tunability of electric properties [113]. On the other hand, Ce6 is an attractive photosensitizing agent with NIR fluorescence emission and deep tissue penetration [114] prone to rapid blood clearance and degradation in physiological conditions [115]. Nanocarriers have shown to be excellent vehicles for transporting Ce6 in

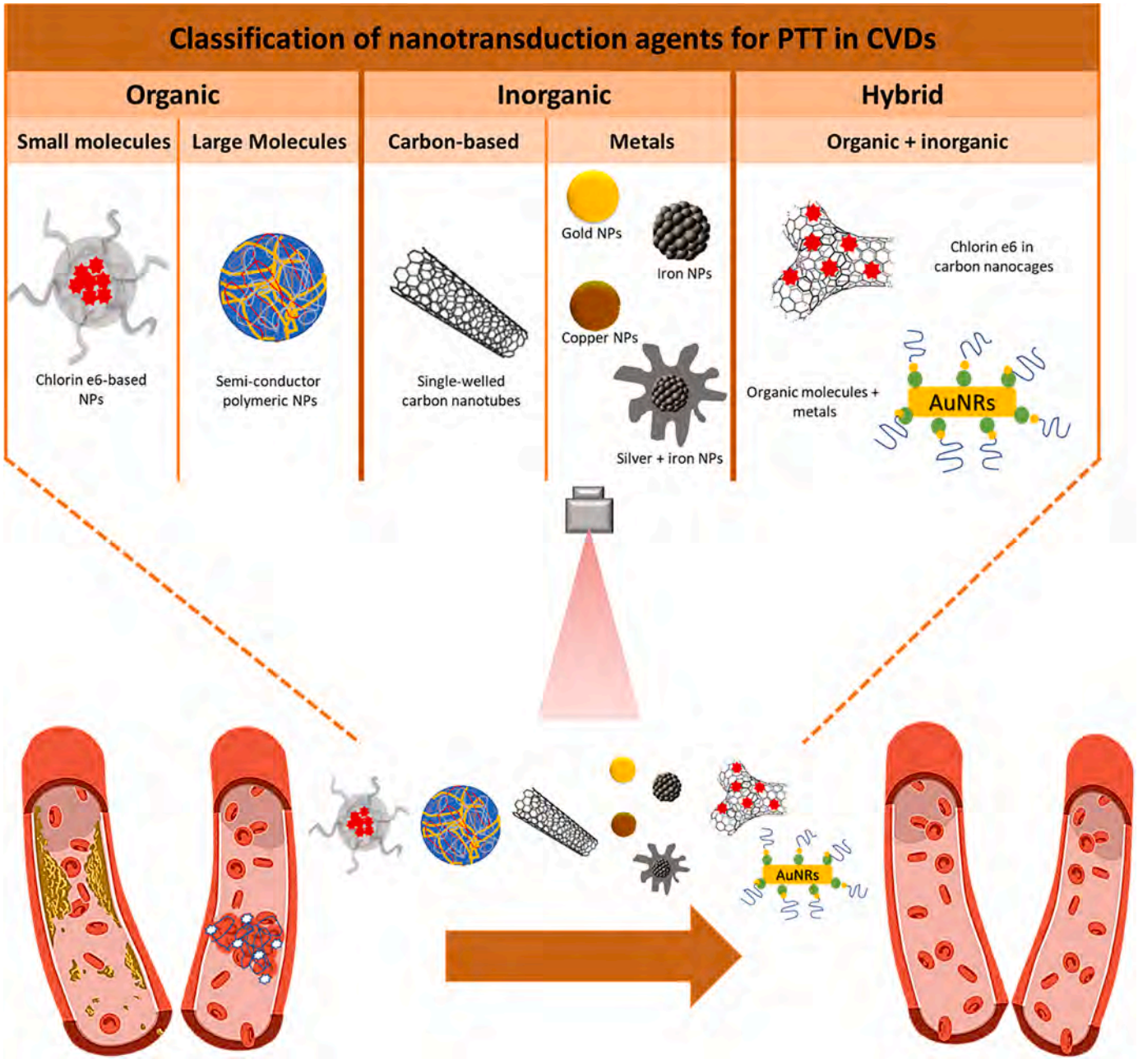

Fig. 2. Classification of transduction nanoagents developed for CVDs. Nanotheranostic PTAs tested in CVDs can be broadly divided into three groups: organic, inorganic, and hybrid nanomaterials combining both. The most explored group in theranostics of PTT for CVDs is the inorganic division. Among this, metal nanoparticles (particularly gold, coper, and iron) are the most studied nano PTAs. Research on organic nanomaterials for PTT with diagnostic abilities is the group requiring more development.

biomedical applications and increase the circulation time of Ce6 in the body [74].

The first organic system we identified is glycol chitosan/heparin-decorated polypyrrole nanoparticles (GCS-PPY-H) for NIR-light-modulated photothermal thrombolysis and fluorescence imaging of thrombosis [76]. These nanoparticles possessed dual targeting glycol chitosan/heparin to target acidic/P-selectin high-expression inflammatory endothelial cells in the thrombus. The second system reported is dextran sulfate conjugated to Ce6 (DS-Ce6) for targeted photoactivation of atherosclerosis [77]. DS of the nanomaterial can specifically bind to the type A scavenger receptor (SR-A) expressed only on the activated macrophages of the arterial plaque. The third system is a similar nanosystem using Ce6 as PTA and dextran sulfide for targeting macrophages in atherosclerotic plaques [78]. Unlike DS-Ce6, this nanosystem also consisted of chitosan-coated carbon nanocages (CS-CNCs) used as nanocarriers of Ce6 and then linked with DS (CS-CNCs@Ce6/DS), aiming at enhancing the photothermal conversion capability of the platform. The carbon served as a PTA to cause hyperthermia and release

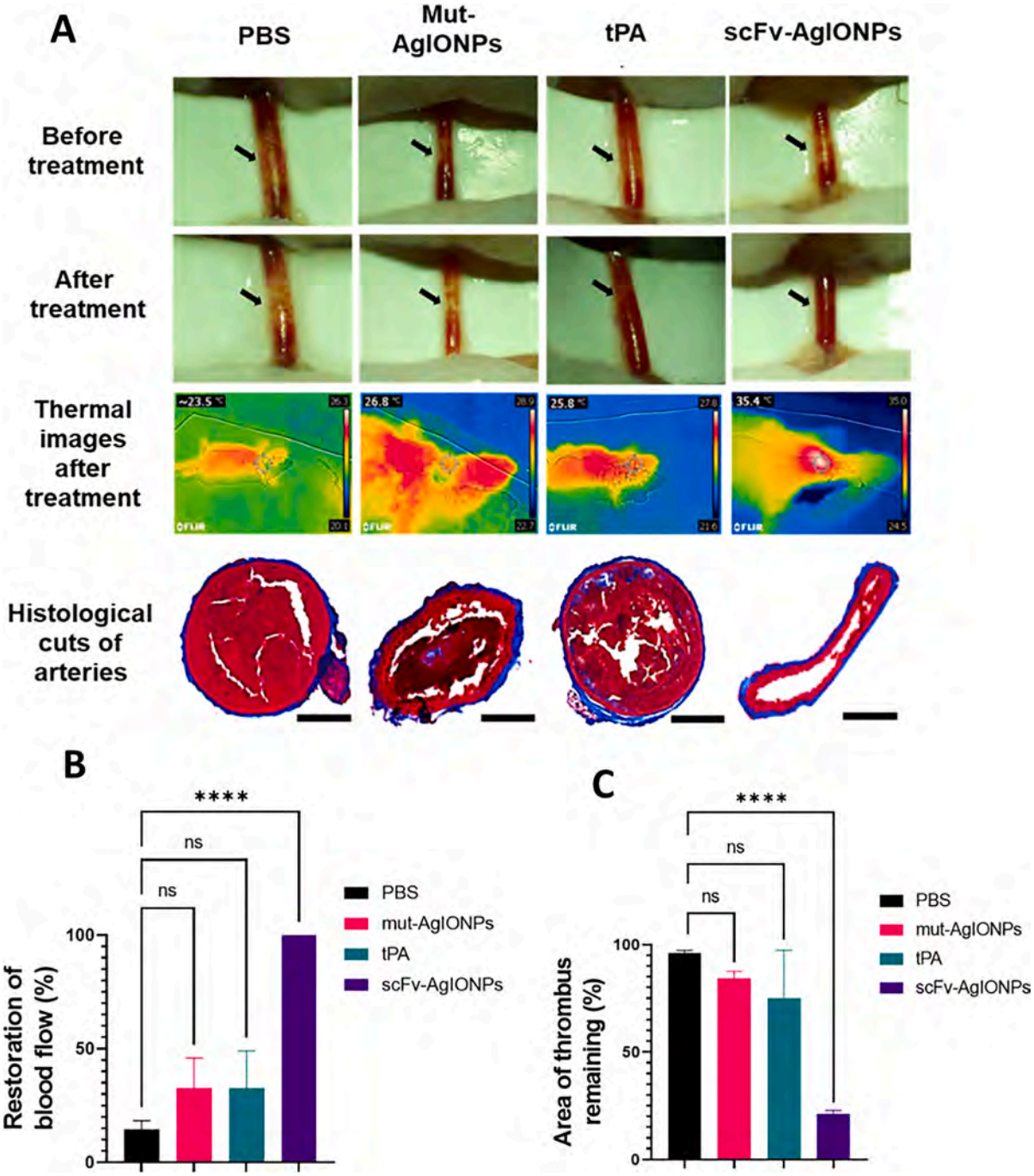

Fig. 3. Photothermal thrombolysis in mice induced by AgIONPs. A) Images from the microscope showing thrombosed arteries (arrow pointing thrombi) before and after laser treatment, suggesting the targeted group had the highest thrombolysis when compared to the other groups. Thermal photos showing the increase in temperature from the last laser cycle of the treatment. *Ex vivo* histological cuts of stained arteries suggesting less thrombus area remaining in the group treated with AgIONPs (thrombus area in red). C) Quantitative analysis using ImageJ of remaining thrombus area in A and B) analysis from blood flow measurements showing significant differences between the groups treated with targeted nanoparticles and no significant differences between the non-targeted or free tPA groups. Taken from Vazquez-Prada et al. [15]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

of Ce6. Ce6 was used as the photosensitizer for PDT. The properties of CS-CNCs@Ce6/DS for synergistic PTT/PDT were explored *in vitro*.

Targeting of GCS-PPY-H was shown by *in vivo* imaging system (IVIS) fluorescence images. PTT of clots *in vitro* showed the greatest thrombolytic effect in clots treated with GCS-PPY-H. *In vivo* experiments were performed by using a $FeCl_3$-induced thrombosis mouse model. IVIS fluorescence images showed a significantly stronger fluorescence intensity in the thrombus area in the GCS-PPY-H group. Vessels from NIR irradiated heparin group showed a slight lysis of the thrombi, whereas NIR irradiated GCS-PPY-H group showed the highest thrombolysis (~20 %) (Fig. 3**A, B**). Immunofluorescence assays suggest that GCS-PPY-H was able to cause thrombolysis by specific binding to P-selectin expressed on the activated platelets (Fig. 3**C**).

The second study in the literature for PTT nanotheranostics of CVDs consisted of a nanomaterial using chlorin e6 (Ce6) as the photosensitizer [77]. Foam cells (RAW264.7 with LPS in the presence of LDL) and RAW264.7 cells activated with LPS demonstrated good intracellular uptake of the nanoparticles. *In vivo* IVFM imaging and histological analysis showed a significant reduction in the plaque area and macrophages when compared to the laser only and non-irradiation control groups.

The main limitation of this study is the lack of evidence showing the biological interconnections with respect to photoactivation. The results presented suggest a potent photoactivation to reduce macrophages in plaques via apoptosis induction. The authors could not determine if the reduction was caused by DS-Ce6 or if it was due to efferocytosis, which is a defective in advanced atheroma [116]. Future work includes designing a method for determining the molecular pathways involved in the process as it is unclear whether the beneficial efficacy of photoactivation is specific to DS-Ce6. Furthermore, follow-up studies testing PTT are needed. PTT was mentioned both in the introduction and discussion of the paper, however no assays were performed to test hyperthermia-induced release of Ce6 or PTT potential of DS-Ce6.

For DS-Ce6 in carbon nanomaterials, NIR laser irradiation of aqueous solutions of CS-CNCs@Ce6/DS produced an increase of ~30 °C, whereas the temperature of PBS solution only increased by ~1.5 °C. Release of Ce6 upon NIR laser irradiation from CS-CNCs@Ce6/DS was confirmed and attributed to the hyperthermia caused by the nanoparticles. Synergistic effects of PTT/PDT were evaluated *in vitro*. Exposure to both 808 nm and 633 nm laser led to death of macrophages for the CS-CNCs@Ce6/DS group, but the order of laser application was important for the therapeutic outcome.

Efficacy of the anti-atherosclerotic activity of the nanosystem was tested in ApoE–/– mice with partial ligation of the left carotid artery. *Ex*

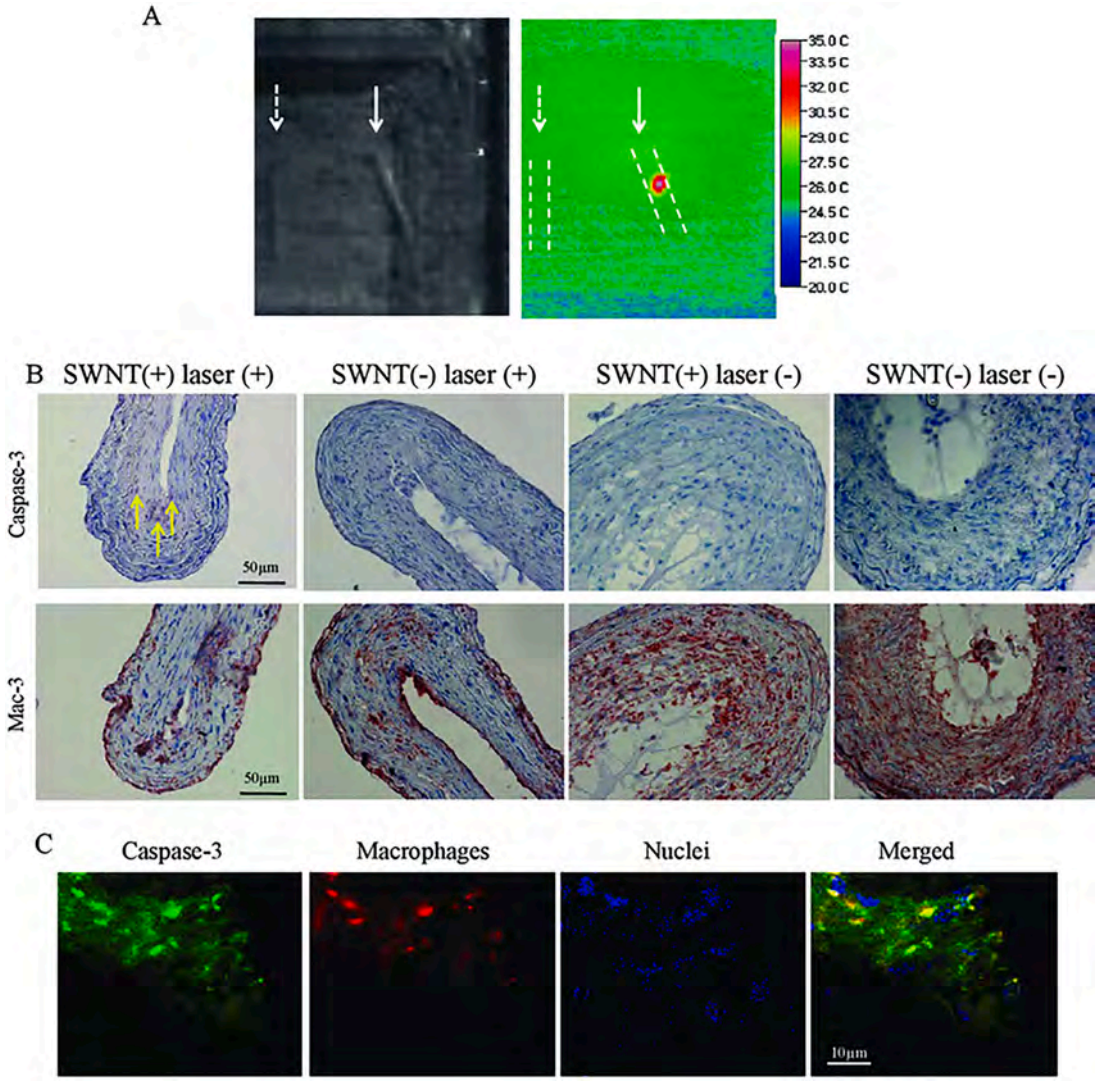

Fig. 4. Ex vivo thermal ablation of atherosclerotic plaque and thermal imaging. A) Brightfield (left) and thermal image (right) of the same showing and increase in temperature of the ligated left carotid artery (arrow) with SWNTs and but not obvious signal in the control artery (dashed arrow). B) Immunohistochemistry for caspase-3 and macrophages demonstrated the apoptosis in arteries treated with SWNTs. Taken with permission and modified from Kosuge et al. [75].

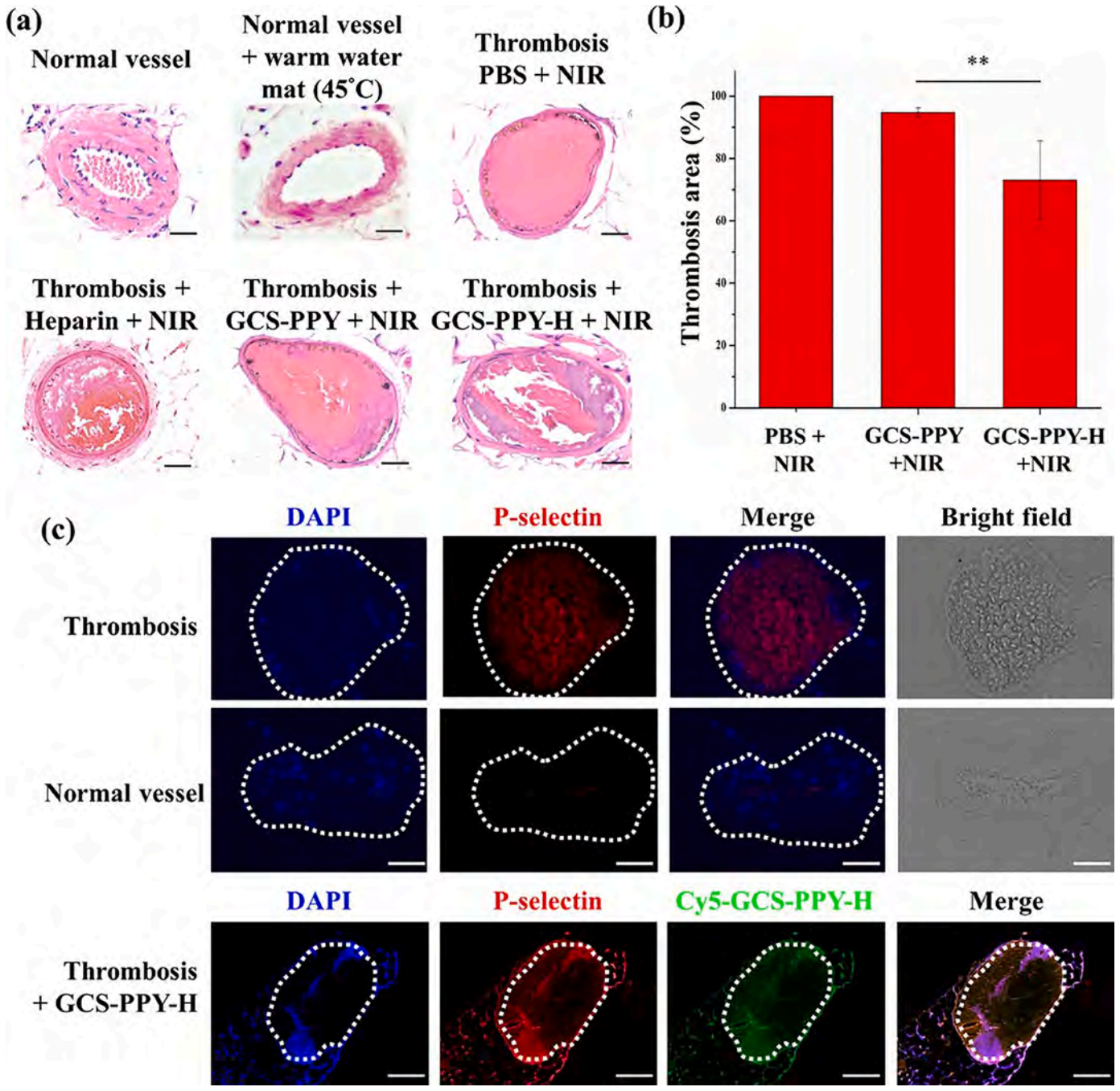

Fig. 5. PTT effect and accumulation of nanoformulations. A) Histology of blood vessels showing thrombi remaining after treatment with the different groups. B) Quantittive data from A.C) Immunohistochemical staining of arteries assessing P-selectin expression or Cy5-GCS-PPY-H $FeCl_3$-induced thrombosis, showing less fluorescence of P-selectin in the treated group than that of the thrombosis control. Moreover, fluorescence signal of GCS-PPY-H can only be observed in the treatment group and correlates with the signal from P-selectin. Scale bar: 30 μm. Retrieved from Lu et al. [76].

vivo NIR fluorescence imaging of the artery confirmed plaque-targeting efficiency of CS-CNCs@Ce6/DS. *Ex vivo* NIR fluorescence signal of carotid arteries at 6 h post-injection was strongest in the carotid artery when compared to vital organs. After exposure to 808 nm laser, the temperature of the irradiated lesion area increased drastically in the carotids of mice injected with CS-CNCs@Ce6/DS. The synergistic therapeutic effects of PTT and PDT were confirmed by a significant decrease of the plaque area in the arteries of CS-CNCs@Ce6/DS + Laser 808/633 treated group. These results altogether suggest stabilization and shrinkage of atherosclerotic plaques due to PTT/PDT efficiency of the CS-CNCs@Ce6/DS.

The methodology of laser treatments presented here has been explored in carotid arteries but may not be feasible for coronary arteries due to limited tissue penetration. Further studies can also explore a novel methodology for treating atherosclerotic plaques in coronary arteries, as atherosclerosis is a systemic condition with a strong relationship between coronary and carotid arterial disease [117].

2.4. Nanotheranostic agents combining metallic and organic materials

For nanotheranostics using PTT for CVDs, there are two nanosystems being explored under this category; i) a nanosystem that aims to combine the individual properties of 5-aminolevulinic acid (ALA) and gold to develop ALA:AuNPs in an attempt to provide synergistic PDT/

PTT of atherosclerosis [79], and ii) a nanoparticle for theranostics of thrombosis combining PTT, anticoagulant, and thrombolytic therapy [80]. The mechanism of action of ALA:AuNPs consisted of the conversion of ALA to protoporphyrin IX (PPIX), which accumulates significantly in atherosclerotic plaques and can be easily tracked due to its fluorescence [118] while gold would serve as the PTA for PTT. The second nanosystem includes a mesoporous silica-coated gold nanorods functionalized with an arginine-rich peptide to promote the adsorption of ICG and fucoidan (Fu) and loaded with urokinase (Uk) (Uk/ICG@-SiAuNRs). Urokinase-type plasminogen activator (Uk) is a thrombolytic used in the clinic that catalyzes the conversion of plasminogen to plasmin, thus stimulating fibrinolysis and degradation of thrombus [119]. On the other hand, fucoidan (Fu) is a polysaccharide known to have anticoagulant properties due to interactions with receptors, such as P-selectin, on the surface of platelets [120]. The theranostic nanosystem targeting P-selectin based on AuNRs was developed for thrombus-targeted co-delivery of Uk, Fu, and indocyanine green (ICG). ICG in this nanocomposite was used as a contrast agent for fluorescence imaging and also a photosensitizer to enhance the photothermal effect of the nanosystem.

ALA:AuNPs were studied in an atherosclerotic model of white male New Zealand rabbits. The conversion ability of ALA:AuNPs to PPIX was first studied. The lower fluorescence in blood from ALA:AuNPs groups was attributed to effective accumulation of nanoparticles on the plaques. Fluorescence images from feces after 24 and 48 h show an increase in fluorescence for the three groups, which indicates elimination of porphyrin from the body. Ex vivo microscope imaging of aortas from the control group had normal thickness and no lipid in the intima layer, while the experimental group exhibited thickness in the intima layer. This study serves as preliminary evidence that ALA:AuNPs accumulate in plaques and could potentially be tracked with fluorescence of PPIX in tissues.

ALA:AuNPs were purposely developed for PDT and PTT, but *in vitro* and *in vivo* studies to test the PDT, PTT, and PDT/PTT performance of the nanoparticles were not evaluated in this study. In a follow-up study from the same group, the efficiency of ALA:AuNPs was tested for PDT and sonodyamic therapy (SDT) of atherosclerosis, but not for PTT [121]. Overall, the results *in vitro* suggest that ALA:AuNPs could be used as an atherosclerosis-selective therapeutic agent. Nonetheless, up to date there are no studies published showing evidence of the nanoparticles as a PTA for PTT of atherosclerosis nor showing its efficiency as a therapeutic agent *in vivo*. Importantly, another property of this nanosystem that has not been exploited yet is the ability of gold as a contrast agent in modalities such as computed tomography and photoacoustic imaging, along with its strong photothermal effect for PTT [84,102].

In the second hybrid nanosystem, thrombolysis assays *in vitro* showed that Fu-ICG@Si-AuNRs and Fu inhibited thrombin-induced platelet aggregation by 67.9 % and 8.5 %, respectively. Blood clot lysis assays further confirmed the thrombolytic activity of the Fu-Uk/ICG@Si-AuNRs. Under 808-nm NIR irradiation, Uk/ICG@Si-AuNRs released Uk by localized hyperthermia and resulted in an enhancement of thrombolysis due to PTT and Uk. The greatest increase of thrombolysis was shown by Fu-Uk/ICG@Si-AuNRs, with a 1.7-fold higher than the control, suggesting high binding ability to thrombi and thrombolytic/anticoagulation ability. Vessels collected from $FeCl_3$ thrombosed mice treated with Fu-Uk/ICG@Si-AuNRs indicated a stronger thrombolytic efficacy attributed to combined enzymatic (Uk)/photothermal thrombolysis and P-selectin-targeting ability. *In vitro* NIR fluorescence, X-ray, and CT imaging performed on the thrombi incubated with Fu-Uk/ICG@Si-AuNRs revealed a higher contrast compared with the control group. Fluorescence signals of ICG show that Fu-Uk/ICG@SiAu accumulated at the thrombosis site in a time dependent manner. Ex vivo data from this study show promising nanotheranostic ability of Fu-Uk/ICG@Si-AuNRs. However, no *in vivo* imaging was performed in this study because of the poor penetration of NIR light through deep tissues and organs. Designing systems that overcome this limitation is crucial for testing the efficiency of the nanosystem *in vivo* and as a potential diagnostic agent that can be translated to the clinic.

2.5. Safety, biodistribution and toxicity

The exponential increase in the usage and research of nanoparticles for every day applications have raised concern on the adverse effects of nanomaterials on human health. Assessing the toxicity of biomaterials is paramount before their translation into the clinic. Before considering any potential therapeutic applications, it is important to investigate the implications of nanomaterial exposure. Parameters such as cytotoxicity, biotoxicity, biodegradation, excretion, and biodistribution need to be evaluated [122].

Enormous efforts have been made towards understanding and addressing the safety of nanomaterials. These efforts focus on ameliorating adverse effects such as cytotoxicity, inflammation, unspecific targeting, aggregation, and immune cell sequestration, among others [123]. There are various characteristic features that will influence a nanomaterial's biocompatibility and how they interact with biological organisms such as their physicochemical and quantum mechanical properties. It has been observed that certain features such as structure, size, shape, and specific surface characteristics [124,125]. Therefore, recent studies are paying special attention to variables affecting safety in the study design and methodologies used for nanoparticle synthesis. Strategies for mitigating adverse events include the use of biodegradable nanomaterials to increase biocompatibility, producing ultrasmall nanoparticles with zwitterionic or positive surface charges, pre-formation of corona *in vitro* or *ex vivo, in silico* modeling strategies [123,126].

The toxicity studies of nanoparticles reviewed here provide promising insights towards the safety of using nanomaterials as PTA for thrombosis and atherosclerosis. Nonetheless, these studies are still limited and have discrepancies from the diversity of experimental designs, type of cells/animals, doses and exposure times used in the experiments. Further research on the interactions of the nanoparticles at preclinical and clinical level are needed to fully understand the effects of nanoparticles.

2.6. Metallic photothermal agents

Cell culture experiments have revealed no apparent short-term (24 h) toxicity from gold nanorods (size range of 5–60 nm and concentration in the range of 0–35 μg/mL) discussed in this review [84–86]. AuNRs showed to be non-cytotoxic for Ana-1 cells and had good compatibility based on histological analysis of vital organs at 20 $\mu g.mL^{-1}$ [84]. RAW264.7 cells incubated with hollow-type gold-nanoparticles demonstrated a decrease in cell viability at 48 h even without laser irradiation when the concentration of NPs rose to an optical extinction density of 4.0 at 808 nm [85]. While it is frequently reported that gold-based nanoparticles show no cytotoxicity, there are *in vitro* and *in vivo* evidence of cellular reactive oxygen species production, mitochondrial toxicity, cytokine release, apoptosis and necrosis [125]. ICP analysis of the biodistribution of AuNRs in the major organs showed that nanorods accumulated primarily in the spleen and liver, suggesting clearance mainly through the renal/urinary route and the reticuloendothelial system (RES) [84].

Silver, iron, and copper-based nanoparticles showed similar results to that of gold-based nanoparticles. A minimal decrease in cell viability of J774A.1 (5–20 %) after 24 h was observed when the cells were incubated with Ag-IO-PAA at 0.1 mg/mL [72]. The biodistribution of Ag@IO-PAA (3.2 mg/kg) in C57BL/6 mice was evaluated over 7 days. ICP studies showed accumulation of Ag@IO-PAA mostly in the spleen and liver. Histological images of organs from treated animals after 1, 3, and 7 days exhibited insignificant pathological changes. These findings demonstrated that Ag@IO-PAA in mice poses no significant signs of toxicity. *In vivo* toxicity at 1, 3, 7, and 10 days of Fe_3S_4 nanoparticles at

12 mg/kg was evaluated by blood bioanalysis, ICP-MS and histological analysis [73]. There was no obvious difference detected in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), indicating Fe_3S_4 nanoparticles have good biocompatibility to the liver and heart. Histological analysis of main organs suggests no tissue damage or adverse effects. ICP-MS analysis found that Fe_3S_4 nanoparticles mainly accumulated at the spleen and liver. CuS-TRPV1 did not cause apparent cytotoxicity in VSMCs with up to 30 laser on/off cycles incubated with or without 0.4 mg/mL of nanoparticles [74]. The biodistribution of CuS-TRPV1 was confirmed by *ex vivo* organ inductively coupled plasma mass spectrometry (ICP-AES) at 2, 4, 24, and 72 h post-injection. The majority of intravenously injected CuS-TRPV1 was taken by the RES. Importantly, the liver uptake gradually decreased at 24 h while kidneys uptake increased, suggesting that small nanoparticles could potentially be renally eliminated from the body.

Future efforts are needed to reduce the capture of metallic-based nanoparticles by the RES, as this could lead to hepatic and splenic toxicity, as observed by Cho et al. [127]. Ideally, nanoparticles should be optimized to be quickly excreted from the vital organs, while being able to effectively accumulate and retain in lesions. Studies increasing the time span of the toxicity assays should also be performed to address the long-term toxicity resulting from metallic-based nanoparticles are needed before their clinical use.

2.7. Non-metallic photothermal agents

Flow cytometry demonstrated that SWNTs alone did not induce apoptosis (0.2 ± 0.002 absorbance units [AU] for SWNT[+]/ light[+]) [75]. The authors report no significant acute or chronic toxicity of SWNTs regarding clinical and laboratory parameters, histology, and survival in mice at 3 to 5 months after injection. On the other hand, GCS-PPY-H demonstrated no significant toxicity to endothelial cells with the reported cell viability of more than 80 % [76]. It is important to note that the concentration tested *in vivo* was not stated in the manuscript. This information is crucial for exploring new strategies to further enhance the thrombolytic effect of GCS-PPY-H *in vivo*. If the concentration of nanoparticles was 600 μg/mL, the ~20 % lysis obtained from this study could be potentially increased by irradiating the vessels with 4 cycles instead of one, similar to conducted *in vitro* studies. This strategy should be performed after a viability study demonstrating that endothelial cells incubated with 600 μg/mL of GCS-PPY-H did not decrease the viability significantly upon 4 cycles of exposure to laser (5 min, 2.45 W/cm^2, off: 3 min). Moreover, *ex vivo* analysis showed that the nanoparticles accumulated in the liver and kidney, possibly owing to their hydrophobicity. No apparent damage of tissue was shown by histology in vital organs.

Macrophages treated with DS, Ce6, or DS-Ce6 without irradiation exhibited negligible toxicity for 24 h even with 6 μg/mL of Ce6 [77]. DS-Ce6 also showed negligible phototoxic effects on Ecs and SMCs, probably due to a significantly low cellular uptake of DS-Ce6 by Ecs and SMCs. Moreover, there was no change in cell viability in activated and non-activated macrophages treated with CS-CNCs@Ce6/DS [78]. Further studies testing cell viability in Ecs should be explored as proof of non-invasiveness of the nanosystem. *Ex vivo* near-infrared fluorescence signal of major organs after 6 h post-injection of CS-CNCs@Ce6/DS showed major accumulation of nanoparticles in the lung and kidney. H&E staining of major organs showed no significant differences between the treated group and the control group. No significant differences were found on liver and kidney functions in atherosclerotic mice treated with CS-CNCs@Ce6/DS. Urine collected during 3 days after intravenous injection showed ~31.7 % of the injected CS-CNCs@Ce6/DS was excreted in the urine. However, this study missed to report the nanoparticle dose that they employed.

2.8. Hybrid photothermal agents

The cytotoxicity of Uk/ICG@Si-AuNRs and Fu-Uk/ICG@Si-AuNRs was evaluated in human umbilical vein endothelial cells cultured with different sample concentrations [80]. Results revealed that nanoparticles did not reduce cell viability at 24 h for up to an equivalent concentration of Uk <1250 U/mL. Notably, cell viability did not significantly differ between the Uk/ICG@Si-AuNR and Fu-Uk/ICG@Si-AuNR groups. Histological analysis of soft tissues indicated no notable inflammatory or injury responses. Biodistribution analysis with fluorescently histological data revealed the fluorescent ICG signals were mainly found in the liver and kidney, suggesting that the hydrophilic nanocomposites are metabolized by the liver and further be eliminated by the kidney.

Whilst no significant toxicity was reported in discussed NP systems, there is still a gap in fully understanding the toxicity effects of metallic, non-metallic, and hybrid photothermal agents for thrombosis and atherosclerosis models. Further long-term studies assessing the metabolic pathways, pharmacokinetics, and interactions with biocomponents will enable a better understanding and are required for their successful clinical translation. In addition, most photothermal agents lack studies testing the toxic effects of nanoparticles under laser irradiation on surrounding cells, tissues, and membranes. Further research on the possible immune and inflammatory processes, and hemocompatibility of these agents are also crucial for determining their potential to be used as safe strategy in real clinical practice.

3. Limitations and challenges in clinical translation

The development of PTAs for photothermal therapy in biomedical research has gained interest because of its spatiotemporal selectivity, high specificity and minimal invasiveness [128]. Nonetheless, PTT is challenged by several factors, hampering the translation of most of the approaches into clinical practice. One of the main limitations of PTT is the thermal damage of normal tissues. Some of the approaches to overcome this drawback include the use of NIR region (pprox.. 650–900 nm) laser excitation, which allows the light to penetrate through soft tissues while having minimum absorption to biological tissues and avoiding loss of energy for the PTA [129]. Moreover, recent efforts have been made to deviate high hyperthermia into ablation therapy with mild hyperthermia. This has been shown by shifting from high laser power into moderate to mild power for either longer periods of time or by performing laser irradiation for short periods of time during multiple cycles, allowing cooling intervals between each cycle. The incorporation of thermal cameras to the laser system is also another approach to monitor and regulate the temperature rise in the lesion and avoid undesirable adverse effects.

The penetration depth of the laser is also one of the main limitation of PTT, as it might lead to insufficient therapeutic effect [130]. It is known that the laser intensity and wavelength used strongly correlates to the penetration depth achieved in the tissue. Laser light with longer wavelengths and higher power penetrates deeper in the body. This is another reason why future studies should focus on PTT with wavelengths in the NIR window. Attempts to boost therapeutic efficiency have also been made by attaching other treatment modalities, such as thrombolytics, to the PTA. One of the key advantages of combined therapy is the opportunity to lower the dose of each therapy and decrease undesirable side effects while achieve similar or even synergistic therapeutic effects via hyperthermia-mediated drug delivery.

Enhancing the accumulation of PTAs in the lesion site with passive or active targeting via conjugation of targeting ligands such as antibodies, peptides, and proteins has also shown to improve therapy outcomes. Combination therapy and the development of theranostic PTT platforms like the ones reviewed here are paramount strategies for expanding PTT into clinical research. The incorporation of imaging agents into PTAs for multiple imaging allows researchers to monitor the accumulation of

PTAs at the lesion site in real time. Imaging-guided therapy enables an accurate diagnosis whilst increase the therapeutic efficiency by improving the precision of the treatment procedure.

Finally, the development and optimization of PTAs are challenged due to the complexity of their synthesis and desired characteristics. An ideal PTA for theranostics using PTT should have strong absorption in the NIR region, excellent photostability, good thermal conductivity, and minimal toxic effects. In addition, the nanomaterials should be easily reproduced and scaled up to increase their potential translation to the clinic. Bridging the *in vitro-in vivo* gap in this domain remains extremely challenging.

Besides the common challenges shared with other diseases such as cancer, nanomaterials for CVD face limitations specific to their pathogenesis and nature. Atherosclerosis, the major pathological cause of CVDs, is characterized for being asymptomatic in early stages of the progression. It is well known that the efficacy of the therapeutic outcome strongly relies on the early detection of the atherosclerotic plaque. This is particularly challenging since atherosclerosis's targeting biomarkers lack specificity as most of them are systemic markers of inflammation [131]. Moreover, most biomarkers currently used for detection of atherosclerosis are present in various developmental stages of the disease and their presence varies depending on patient's characteristics such as age or ethnicity [132]. Thus, there is a need for using novel technologies such as genomics, lipidomics and metabolomics to find new robust biomarkers able to indicate progression of atherosclerosis.

Specific to nanoparticles designed for theranosis of thrombosis is the need to reduce haemorrhagic risk. Most therapeutic approaches of theranostic nanomaterials achieve thrombolysis through the delivery of thrombolytics and anticoagulants. It is of particular interest that these drugs limit their release to the thrombus area. Non-specific release of the drugs or surface loading of the therapeutic onto the nanoparticle need to be avoided to decrease bleeding risks [133]. Therefore, future studies should focus on designing nanosystems with the therapeutic loaded in the core and specific delivery to the thrombus. Specific delivery is being achieved by active targeting to main components of thrombi such as activated platelets and fibrin [15]. Nonetheless, the thrombus microenvironment, local shear stresses, and the need of rapid targeting before full occlusion of the blood vessel make it difficult to target nanoparticles efficiently to the desired site [134]. To overcome this, new strategies are being developed to speed accumulation of the nanomaterial at the thrombi and to enhance the penetration into the clot [133].

The field of nanotheranostics for atherosclerosis and thrombosis using PTT as the therapeutic approach is still in its nascent stages and the full potential of clinical impact is not yet explored. While research in the field is expanding and there have been promising insights towards translational nanosystems, these challenges still need to be addressed before moving from bench to bed.

4. Summary and outlook

PTT using NIR is a promising treatment modality for atherosclerosis and thrombosis owing to its high therapeutic efficacy, deep penetration, non-invasiveness, and minimal side effects. Although research in the area is just emerging, the preclinical evidence so far shows promising results on the effectiveness of PTT for biomedical applications. The outcome of PTT is highly dependent on the properties of the transducer. Nanomaterials hold good potential as PTAs and have excellent capability for theranostic approaches, thus enabling photothermal-guided therapy. Enhancement of therapeutic efficacy can be obtained through several strategies, including combination of materials with diverse abilities and functionalization with targeting moieties to ensure the successful delivery of the agent. Moreover, combining PTT with drugs used in the clinic such as anticoagulants and thrombolytics can significantly increase the therapeutic ability due to potential synergistic interactions.

In this review, we have summarized the recent developments in nanotheranostic PTT of atherosclerosis and thrombosis. A literature search across three databases (Google Scholar, PubMed, Science Direct) was performed to identify all English-language articles using nanomaterials for diagnosis and PTT of cardiovascular disease. The methodology was designed to include all articles that tested at least one imaging modality either *in vivo* or *in vitro,* and that used PTT as the therapeutic approach for treating any cardiovascular disease. Keywords for performing the search included: "photothermal therapy", "photothermal ablation", "cardiovascular disease", "theranostic", "hyperthermia", "thrombolysis", "thrombosis", and "atherosclerosis". We evaluated and screened these results for articles that met both criteria: the diagnosis and PTT approach. Articles that did not showed diagnosis evidence, did not use nanomaterials or that used any other approach for treatment strategy other than PTT were not reviewed herein. Most of the work in the field for CVDs that we found using this methodology was done in metallic PTAs and only for atherosclerosis and thrombosis, constituting 77 % and 33 % of the research reviewed here, respectively.

Out of the 15 articles that met the criteria for this review, 8 of them have been published within the last five years. Out of these 8 articles, 7 have been published since 2021. In addition, the very first preclinical *in vivo* study reported for theranostic photothermal nanomaterials for CVDs was published in 2012. Research in this field is still on its early stages, especially compared with similar fields such as cancer nanomedicine. In fact, we identified about 350 clinical trials assessing nanoparticles for treating cancer, whereas clinical trials testing CVD nanomaterials were scarce (only 25) [135]. Follow-up preclinical studies are just starting to rise. Interestingly, there are even clinical trials using gold-silica nanoparticles for photothermal therapy of atherosclerosis. So far, data has shown the nanoparticles had better efficiency in reducing atherosclerotic plaque than stents [136]. If the tendency continues, within the next years we might be able to read more follow-up studies and maybe even more clinical trials using theranostic nanoparticles for CVDs.

There are still several challenges that need to be addressed, including the development of novel and dual- or multi-modality nanotheranostics, and the design of experiments to test their efficiency *in vitro* and *in vivo*. The use of PTT for other diseases (*i.e.*, cancer) has been studied extensively, providing several candidate materials that have not been tested yet for CVDs. Repurposing some of these nanosystems for treatment of CVDs may be promising. Recent advances in photosensitizers that have been evaluated for nanotheranostics of CVDs also combine other light-triggered therapeutic (PDT) and diagnostic modalities (PAI), such as IR780 [137,138]. These combinations have so far shown promising synergistic effects and may be the basis towards a new branch within nanotheranostics. Importantly, toxicity studies to confirm safety need to be evaluated before the nanomaterials can be used as biomaterials for PTT. Most of the studies reviewed here lack endothelial cell viability assays to corroborate the non-invasiveness of the nanosystems and the specific laser settings used for each study. Endothelial cells are the main component of the endothelium, a thin membrane that lines the inside of the heart and blood vessels. Performing viability studies of endothelial cells is fundamental to provide insights towards the toxicity effects that the nanomaterials and the laser treatment possess towards surrounding tissues.

It is important to note that most nanomaterials developed for theranosis of CVDs have NIR-1 peak emissions (700–1000 nm). There is an extremely limited number of nanomaterials with NIR II (1000–1700 nm) peaks developed for visualization of thrombi or atherosclerotic plaques, yet alone for theranosis using PTT, hence why we barely covered these nanomaterials herein [139,140]. The few NIR II nanomaterials reported in the literature have not been used for theranosis of CVD. Some of the reasons why the use of NIR II nanomaterials is still limited include that i) they can only afford indirect visualization of thrombi or occlusions in the vessels, ii) they are inorganic nanomaterials and small molecule dyes, which may have possible long-term toxicity,

iii) materials need to have higher absorption and extinction coefficient to be able to make the most out of the NIR II light [139,140]. Nonetheless, NIR II nanomaterials are still of interest since NIR II light has deeper tissue penetration depths, which translated to a higher sensitivity and better spatiotemporal resolution [141]. Current research is focused on improving the biocompatibility, photothermal conversion efficiency, absorption and extinction coefficient of nanomaterials triggered by NIR II light [142,143]. Materials in the NIR II are therefore expected to have faster development and a broader application in the next few years, including their use as theranostic agents for CVD.

Altogether, this review provides insights on the strategies that could serve as nanotheranostic PTAs or are yet to be studied for PTT of CVDs. Comparing the efficacy and utility of these systems based on their reports is not straightforward, as some of the studies did not perform photothermal conversion experiments or lack vital information such as laser intensity, time of exposure, and even concentration of nanomaterials used. Even when they provide all this information, the methodology such as laser wavelength used and the units of its intensity differ. A key challenge in the field is the standardization of assays and techniques for comparing efficacy within CVDs. An alternative to setting up standards would be a large-scale collaborative comparative study. Such approaches will enable comparability of the distinct nanosystems and ensure an easier transferability towards clinical applications. A key challenge for research on nanotheranostic PTT for CVDs is the lack of follow-up preclinical studies, especially when preliminary data suggest promising results. This lack of progression delays the advancement of basic science and therefore its translation to the clinic. CVDs are still the leading cause of morbidity and mortality worldwide so it is paramount and a priority for this field to continue on nanomaterials aimed to treat them.

Despite the limited research on nanotheranostics for PTT of CVDs, recent reports show promising insights that suggest this could be an alternative non-invasive approach for treating and diagnosing CVDs.

CRediT authorship contribution statement

Karla X. Vazquez-Prada: Conceptualization, Investigation, Visualization, Formal analysis, Writing – original draft. **Shehzahdi S. Moonshi:** Writing – review & editing. **Zhi Ping Xu:** Supervision, Writing – review & editing. **Hang Thu Ta:** Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Data availability

No data was used for the research described in the article.

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