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Polydopamine-based nanostructures: A new generation of versatile, multi-tasking, and smart theranostic tools

Matteo Battaglini [a,*], Melis Emanet [a], Alessio Carmignani [a], Gianni Ciofani [a,*]

[a] Istituto Italiano di Tecnologia, Smart Bio-Interfaces, Viale Rinaldo Piaggio 34, Pontedera 56025, Italy

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ABSTRACT

Smart nanomaterials, thanks to their stimuli-responsive properties, represent a promising class of nanostructures for biomedical applications. Their ability to undergo structural or functional changes in response to specific external cues has been exploited for the manipulation of cellular activities as a potential treatment for various health disorders. Despite their rather interesting properties and applications, most smart nanostructures are composed of inorganic materials, thus limiting their translatability in clinical applications due to potential toxicity and long-term accumulation concerns. Polydopamine nanostructures can overcome the limitations posed by inorganic smart nanomaterials thanks to their high biocompatibility, biodegradability, antioxidant effects, pH-responsiveness, tunability, surface reactivity, photothermal conversion properties, and the ability to act as photoacoustic contrast agents. In this review, we will present a general analysis of the properties of polydopamine nanostructures and of their biomedical applications. Our aim is to provide the reader with the state of the art concerning the use of polydopamine nanostructures as smart organic nanoplatforms in nanomedicine, also providing an analysis of the current limitations connected to the translation in clinical applications and the potential solutions to these challenges.

Introduction: The potential of polydopamine nanoparticles as an organic theranostic smart nanoplatform

Theranostic refers to the possibility of combining diagnosis and therapy into a single platform [1,2]. Since the introduction of the term in 1998 by John Funkhouser, theranostic nanomaterials have gained great attention as a potentially revolutionary tool in medicine, promising to bypass the limitation of conventional diagnostic and therapeutic approaches and being able to provide a faster, cheaper, safer, and more effective intervention on health disorders [1,2].

Smart nanomaterials represent one of the most promising classes of nanomaterials among the various types of theranostic nanoplatforms [3,4]; they are able to change their structural or functional properties in response to specific external stimuli such as temperature, pH, light, magnetic fields, and electrical or mechanical stimulation [3,4]. Some of the most representative examples of smart nanomaterials include iron-based magnetic nanoparticles such as superparamagnetic iron-oxide nanoparticles (SPIONs) [5], piezoelectric nanostructures such as barium titanate nanoparticles [6,7] or boron nitride nanotubes [8], and light-responsive noble metal nanomaterials like gold nanoparticles [9]. The rationale behind the use of smart nanomaterials is to exploit their ability to respond to external stimulation to achieve a desired biological effect that can range from a controlled tuning of specific cellular activity, such as neuronal activation [6] or muscle cell contraction [9], to the inhibition of cancer cell proliferation and induction of apoptosis [5]. The desired biological effects can also be achieved by combining external stimulation with specific molecular cargos, like in the case of drug-loaded nanoparticles for the magneto-thermal or photothermal therapy (PTT) of various forms of cancer [5,10].

The diagnostic components of smart theranostic nanoplatforms are linked to the possibility of exploiting inorganic nanostructures as contrast agents in various detection techniques: for example, magnetic nanostructures in magnetic resonant imaging (MRI) [11] or noble metal and barium titanate nanoparticles through computed tomography (CT) [12,13]. However, the diagnostic potential of smart nanomaterials can be improved with the labeling with specific compounds like fluorescent dyes, MRI contrast agents (for example Gd-based compounds), or radioisotopes for single photon emission computed tomography (SPECT) or positron emission tomography (PET) [14].

* Corresponding authors.
E-mail addresses: Matteo.battaglini@iit.it (M. Battaglini), Gianni.Ciofani@iit.it (G. Ciofani).

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Despite their interesting properties, the adverse health effects related to the use of inorganic nanomaterials have raised concerns among the scientific community. The potential toxicity of inorganic nanomaterials is an extremely complicated problem that is highly dependent on several factors, including the size and physical/chemical properties of the exploited nanostructures [15–17]. Moreover, the inability of most inorganic nanomaterials to be biodegraded and excreted from tissues has been linked to the onset of potential adverse health effects [15–17]. Lastly, the fabrication of inorganic nanomaterials usually involves the use of organic solvents and other potentially toxic compounds able to induce adverse effects in cells and tissues if not properly removed after the nanostructure synthesis [18]. A possible solution to overcome the limitations of inorganic nanomaterials would be the development of organic biodegradable smart nanostructures able to be synthesized without the need for toxic reagents. In this view, polydopamine nanoparticles (PDNPs) represent an extremely promising candidate as a smart organic, biodegradable, and highly biocompatible nanomaterial [19,20]. Described for the first time in 2007 by Lee *et al.*, polydopamine is a material derived from the self-polymerization of dopamine, inspired by the adhesive components excreted by the mussel *Mytilus edulis* and commonly used as a coating material due to its adhesive properties and relatively high biocompatibility [21]. In the following years, the synthesis of nanostructures composed of polydopamine, primarily PDNPs, catalyzed great attention because of their several interesting features (Fig. 1):

1) PDNPs are completely organic and can be synthesized without using organic solvents or other potentially toxic compounds. Moreover, they have been shown to be highly biocompatible even at relatively high doses [19,20];
2) PDNPs are biodegradable and can be easily excreted from tissues [22];
3) PDNP size, porosity, and shape can be tuned with relative ease by changing specific parameters of their synthesis procedure, including temperature, pH, or monomer concentration [23–25].
4) due to the functional groups present on their surface (catechol, imine, and o-quinone), PDNPs can be easily functionalized with a vast variety of molecules [20,26];
5) PDNPs can convert light irradiation at specific wavelengths (in particular in the near infrared -NIR-) into heat, enabling their exploitation as platforms for PTT [27];
6) PDNPs have antioxidant properties, being able to scavenge a vast variety of reactive oxygen species (ROS) from the surrounding environment, because of the previously mentioned functional groups present on their surface [28,29];
7) PDNPs are inherently pH-responsive, and this property can be exploited to achieve the targeted delivery of active molecules (e.g., drug release from PDNPs triggered by the acidic pH environment typical of the tumor niche) [30];
8) Lastly, it has been observed that PDNPs can be used as label-free photoacoustic (PA) contrast agents, enabling the imaging of biological structures [31].

The interest in polydopamine-based nanomaterials is demonstrated by the ever-increasing number of scientific articles present in the literature discussing the synthesis and exploitation of PDNPs. Moreover, several reviews already discussed the properties and potential applications of PDNPs [19,20,26], however focusing either on specific applications of PDNPs or on their potential use in combination with inorganic nanomaterials (for example SPIONs or gold nanostructures) [19,20,26]. In this review, we aim to provide a complete analysis of PDNP properties, synthesis procedures, and biomedical applications focusing our discussion on studies exploiting completely organic formulations of PDNPs. Our goal is to demonstrate how polydopamine represents to date one of, if not the most, promising candidate for the development of organic biocompatible and biodegradable smart nanoplatforms, able to overcome the limitations posed by inorganic smart nanomaterials. With this work, we hope to further trigger the scientific community towards new and clinically translatable applications of PDNPs, paving the way to their realistic exploitations in human healthcare.

Fabrication procedures and properties of polydopamine nanostructures

Synthesis of polydopamine nanostructures

There are currently three main ways to fabricate polydopamine-based materials, namely solution oxidation [32],

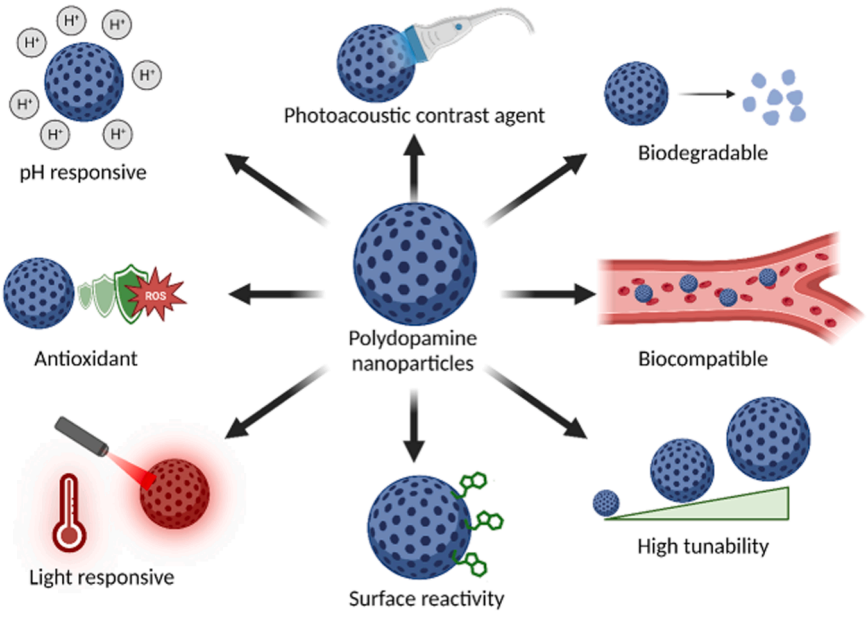

Fig. 1. An overview of the "smart" properties of PDNPs.
Image prepared with www.Biorender.com.

electro-polymerization [33], and enzymatic oxidation [34]. The solution oxidation procedure is based on the polymerization of dopamine under alkaline conditions (pH>7.5) [20,35]; electro-polymerization exploits the generation of polydopamine from the direct deposition of dopamine on electrodes [33], while the enzymatic oxidation procedure is based on the preparation of polydopamine by using enzymes such as urease [34]. Among these synthesis procedures, the solution oxidation method represents the easiest to set up, fastest, and most versatile, thus resulting by far the most widely exploited approach [20,35].

Despite the relatively easy synthesis procedure involved in the preparation of PDNPs, the molecular mechanisms at the base of polydopamine polymerization are still largely unknown [36]. The first proposed polymerization model for polydopamine formation is based on the synthesis of melanin in living organisms, where dopamine undergoes a series of oxidative reactions generating 5,6-dihydroxyindole that, in turn, undergoes a series of covalent polymerization processes [36]. As depicted in Fig. 2, under alkaline conditions in solution, dopamine is oxidized in dopaminequinone, which is then subjected to intramolecular cyclization and oxidation to form dopaminechrome; the latter eventually undergoes an intramolecular rearrangement to form 5,6-dihydroxyindole [36]. It was supposed the covalent oxidative polymerization of 5,6-dihydroxyindole being the only process at the basis of polydopamine formation; however, it has been later on demonstrated that the physical self-assembly of non-covalently bonded molecules such as

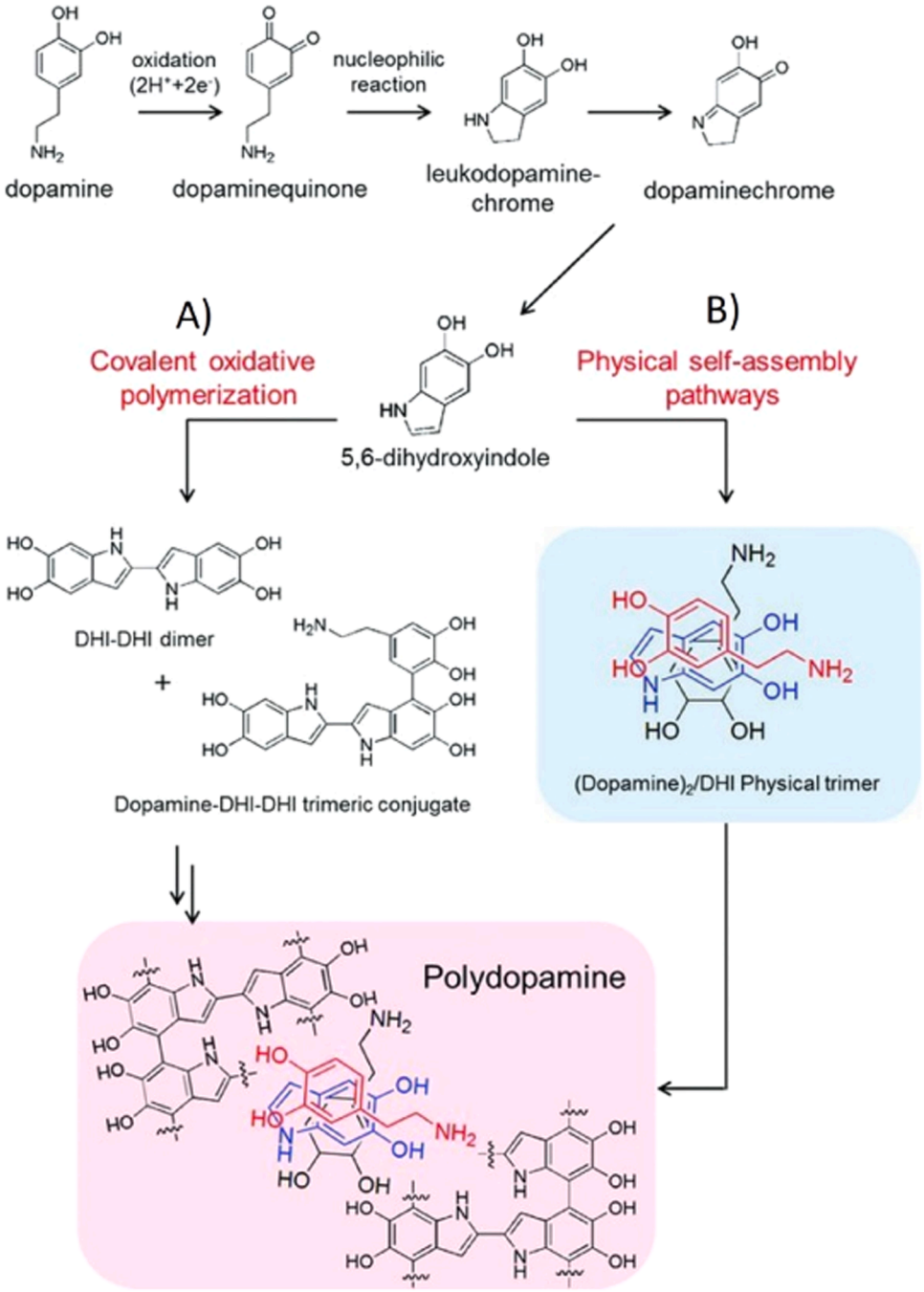

Fig. 2. The two main proposed mechanisms for the formation of polydopamine. A) covalent bond-forming oxidative polymerization; B) physical self-assembly of dopamine and 5,6-dihydroxyindole (DHI).
Image reproduced with permission from Ref. [36].

(dopamine)$_2$/5,6-dihydroxyindole, due to intermolecular interactions like $\pi - \pi$ stacking or hydrogen bonding, could also participate in the formation of polydopamine [36]. Currently it is accepted that both processes are involved in the final formation of polydopamine, yet the precise molecular mechanisms and the final chemical composition of polydopamine-based nanostructures would need further clarifications [36].

Regarding the solution oxidation procedure for PDNP preparation, several parameters of the synthesis process can affect the reaction kinetics and the properties of the obtained nanostructure: pH, solution buffer, temperature, dopamine concentration, and presence of external oxidants [19]. Our group recently demonstrated that by varying the pH of the synthesis solution it is possible to control the size of the obtained PDNPs, with more alkaline pH yielding nanostructures with smaller diameters [24]. Moreover, changing the pH of the synthesis solution has been shown to affect also the kinetics and the yield of the fabrication process, with a more alkaline pH leading to a faster reaction and increasing the yield in terms of obtained PDNPs [37]. The solvent used in the synthesis procedure is commonly just water added with dopamine and a basis; however, it has been shown that buffer solutions such as TRIS-buffer, phosphate, and bi-carbonate can also be exploited, with a direct effect on the size of the obtained nanostructures [38].

Temperature plays also an important role in the synthesis of PDNPs, with temperatures higher than 40 °C increasing the nanoparticle yield but reducing their diameter [39,40]. Dopamine concentration is also an important parameter affecting the kinetic and yield of polydopamine formation; however, most studies in the literature currently describe the effects of dopamine concentration on the formation of films or coating of other kinds of nanostructures rather than in the fabrication of PDNPs [41].

The most common oxidant used for the synthesis of PDNPs is oxygen dissolved in the reaction solution; however, other oxidant compounds have been tested in the polydopamine fabrication process such as Cu^{2+}, $KMnO_4$, Fe^3, $(NH_4)_2S_2O_8$, $NaIO_4$, and $CuSO_4$ [19,42,43]. Despite their exploitability, the use of these alternative oxidants is still limited to the deposition and production of polydopamine films, with oxygen still being the far most used oxidative agent in PDNP preparation [19,42,43].

The diameter of PDNPs is a key factor in determining their properties: for example, it has been observed that smaller PDNPs have a higher antioxidant ability compared to larger nanostructures, a phenomeno due to the increased surface-to-volume ration at smaller sizes [24]. Conversely, PDNPs with larger diameters have been observed to perform better as photothermal conversion agents, being able to generate higher increments in temperature compared to smaller nanostructures irradiated at the same experimental conditions [24]. This difference is essentially due to a higher light absorbance extent by larger nanoparticles [24]. The size of PDNPs has been shown to also affect their stability in aqueous solutions, with larger nanostructures being overall less stable and having the tendency to aggregate and precipitate [24]. Lastly, PDNP size can affect their interaction with biological structures; for example, it has been observed that smaller PDNPs are more easily internalized by cells compared to larger nanoparticles [24]. Moreover, PDNP diameter also plays a pivotal role in cellular uptake mechanism, with smaller PDNPs (180 nm) being internalized through micropinocytosis, while larger PDNPs (520 nm) being uptaken through caveolae-mediated endocytosis [44].

Other features of PDNPs, including shape or porosity, can be tuned by changing their synthesis parameters. For example, mesoporous and hollow PDNPs, recently proposed as alternatives to solid PDNPs due to superior cargo-loading efficiency, can be easily obtained through the classic solution oxidation synthesis procedure of polydopamine by simply adding removable templates and emulsifiers to the reaction mixture [45,46]. Huang *et al.* proposed an interesting protocol to obtain mesoporous PDNPs of various shapes and porosity through Pluronic micelle-guided polymerization [47]. The principle behind this method consists of adding various concentrations of Pluronic F127 and P123 to the synthesis reaction. The added Pluronic is able to self-assemble into micelles acting as templates for the polymerization of mesoporous PDNPs of various shapes while being easily removable at the end of the synthesis through centrifugations and washing procedures [47]. Hollow PDNPs can instead be obtained through various methods such as mini-emulsion templating with organic solvents or by exploiting soft templates such as Pluronic F127 or 1,3,5-trimethylbenzene (TMB) [48,49]. Polydopamine-based nanostructures of different morphologies can also be obtained through oxidation-based synthesis. For example, Sun *et al.* described a detailed protocol to fabricate polydopamine nanobowls of various shapes and diameters obtained through the collapse of hollow polydopamine nanostructures, by exploiting an oxidation-base synthesis in presence of tris(hydroxymethyl)-aminomethane. Hollow bowl-shaped nanostructures of different diameter and wall-thickness were also obtained by simply changing the reaction time [50]. As another relevant example, Yu *et al.* proposed the synthesis of polydopamine nanofibers by conducting an oxidation-based fabrication of polydopamine in presence of folic acid [51].

Biocompatibility, degradation, surface reactivity, and functionalization of polydopamine nanostructures

PDNPs, being derived from polydopamine and mimicking the structure of melanin, are highly biocompatible, and most studies present in the literature confirm the absence of toxic effects after exposure to PDNPs even at relatively high concentrations both in vitro and in vivo [52]. Indeed, polydopamine is commonly exploited to perform a coating and thus to improve the biocompatibility and reduce the toxicity of other compounds like gold nanostructures [53] or zinc oxide nanoparticles [54]. The biodegradation of PDNPs is still a controversial point: it has been observed that melanin films (analogous to polydopamine) implanted in rats were completely degraded after 8 weeks from the implant [55]. Moreover, several external stimuli, including exposure to ROS or alkaline and acidic pH, have been shown to degrade PDNPs [22,24,56]. For example, our group recently demonstrated that the exposure of PDNPs to acidic pH (4.5) and H_2O_2 was able to cause PDNP degradation [24]. Furthermore, the degradation kinetic of PDNPs is once again highly dependent on the properties of these nanostructures, i.e., their size, with smaller nanoparticles being able to degrade faster than larger ones when exposed to high levels of ROS [24]. Our analysis was performed by exposing PDNPs to a solution of 5% hydrogen peroxide (H_2O_2), demonstrating a significant reduction of the average nanostructure size and light absorption properties after 72 h of exposure [24]. Other external stimuli have also been shown to be able to induce PDNP degradation: for example, it has been demonstrated how polydopamine can be degraded through exposure to glutathione (GSH). Dai *et al.* showed how the exposure of PDNPs to 5 mM of GSH for 24 h was able to significantly reduce their average diameter [57]. Del Frari *et al.* demonstrated how polydopamine films could be degraded by exposure to sodium hypochlorite, and how this degradation process is highly influenced by the film thickness and fabrication process [58]. Even physical stimulation, like the exposure to ultrasounds, has been shown to induce PDNP exfoliation, and this process has been used to produce ultrasmall PDNPs (with an average diameter below 10 nm) [29]. However, despite these preliminary results, very little is known about the molecular processes guiding PDNP degradation and the presence and composition of polydopamine degradation products. Moreover, an in-depth analysis of the degradation kinetics of PDNPs inside living organisms is still lacking.

In addition to high biocompatibility and biodegradability, one of the most interesting properties of polydopamine is given by the high reactivity of its constituent monomer dopamine, which makes the surface functionalization of polydopamine-based nanomaterials relatively fast and easy. As described in 2007 by Lee *et al.*, the catechol groups present on the surface of polydopamine can react under oxidizing conditions with thiols and amines via Michael addition or Schiff base reactions [21,

59]. This phenomenon can be exploited to functionalize PDNPs with proteins and other thiol or amine-rich molecules, without the need for any other reagent. An overview of the chemical processes involved in the functionalization of polydopamine with thiol or amine-rich molecules is provided in Fig. 3.

Polydopamine nanostructures as drug carriers

Traditional chemotherapy, despite representing one of the major systemic treatments of cancer, is severely limited by its low targeting efficiency; the off-target distribution of classical drugs reduces the success rate of chemotherapy even potentially leading to systemic toxicity, due to the tendency of commonly used drugs to accumulate in the reticuloendothelial system and in other excretory organs [60]. These considerations are not restricted to chemotherapy, yet they are also valid for other treatments, such as those ones for neurodegenerative diseases [61]. To overcome these limitations, the exploitation of nanocarriers has become one of the main strategies to improve the stability, bioavailability, and targeting efficiency of drugs [62].

Smart nanomaterials loaded or functionalized with drugs, due to their previously mentioned ability to respond to external stimulation, have been proposed as platforms for the targeted delivery and controlled release of bioactive molecules [63]. In this view, PDNPs represent an obvious promising drug delivery tool because of the already described peculiar chemical and physical properties [64]. As previously mentioned, thiol and amine-rich molecules can be easily functionalized on the surface of PDNPs through Michael addition or Schiff's base formation [65]. Moreover, several drugs with anthraquinone structures like doxorubicin, mitoxantrone, epirubicin, idarubicin, and valrubicin can be loaded inside PDNPs or adsorbed on the surface of polydopamine nanostructures through weak molecular interactions (π-π conjugation or hydrogen bonding) [35,66]. The drug loading efficiency of PDNPs can be easily tuned by changing the physical parameters of polydopamine nanostructures such as shape, size, and porosity. For example, as we previously mentioned, it has been shown that mesoporous and hollow PDNPs are able to outperform solid polydopamine nanostructures in terms of drug-loading efficiency [46].

In a recent example, PDNPs were exploited for the oral administration of gambogenic acid (GNA@PDNPs), a traditional Chinese medicine well known for its anti-tumor activity. To improve the cancer-targeting efficiency, folic acid was conjugated on the surface of the polydopamine nanostructures (GNA@PDNPs-FA) [67]. Moreover, since orally administered pharmaceutical agents are absorbed by the gastrointestinal mucosa after passing through the esophagus, the authors coated GNA@PDNPs-FA NPs with sodium alginate (GNA@PDNPs-FA-SA) in order to protect the nanostructures from the harsh physiological conditions of the gastric tract. The authors tested the cumulative drug release of GNA@PDNPs-FA-SA in simulated gastric fluid and intestinal fluid demonstrating the ability of the nanoplatforms to steadily pass through the gastrointestinal environment via oral administration, thanks to the protective effect of the sodium alginate coating. Moreover, in vivo tests on breast cancer-bearing mice showed the higher anti-cancer efficiency of GNA@PDNPs-FA-SA compared to free gambogenic acid [67].

In another example, PDNPs were exploited for the delivery of retinoic acid (RA) [68]. RA, a metabolic intermediate of vitamin A, is widely used in the treatment of melanoma and squamous cell carcinoma; however, its application is severely limited by serious side effects, especially in the case of intravenous administration [69]. In order to avoid such issues, its intradermal administration through skin-specific delivery strategies has been proposed. In this context, PDNPs have been exploited as potential candidates for intradermal delivery of RA,

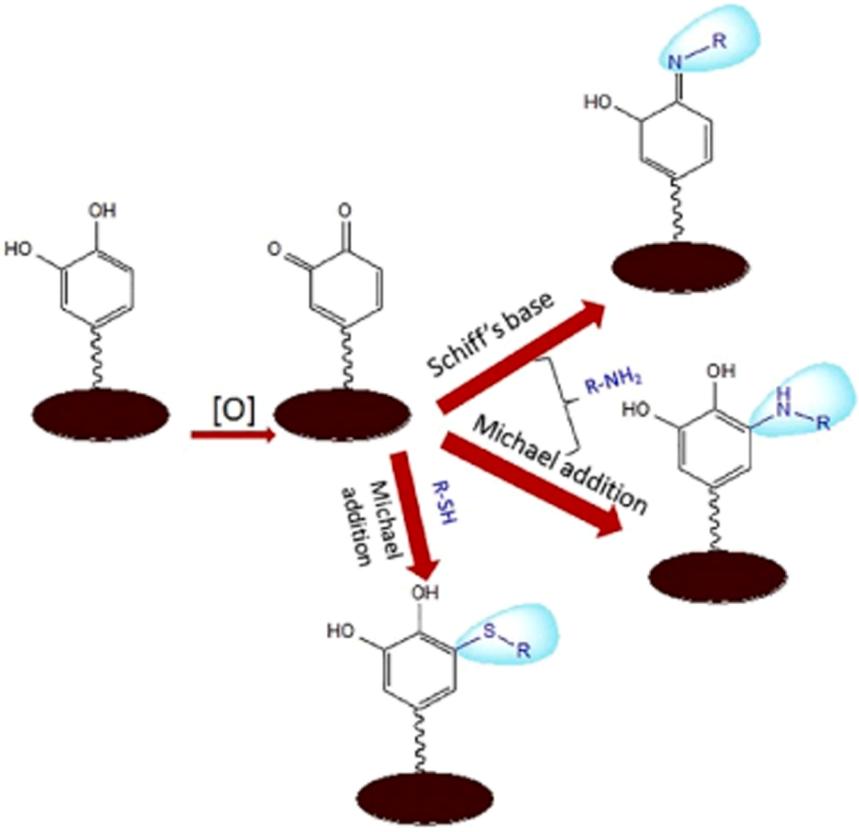

Fig. 3. Surface reactivity of polydopamine: the reactive functional groups present on the surface of polydopamine-based structures can react through Michael addition or Schiff's base reactions with thiol and amine-rich molecules.
Reproduced with permission from Ref. [59].

considering their tissue adhesiveness and skin affinity [68]. In a recent study, free RA and RA-loaded solid and mesoporous PDNPs were tested on rat skin models, comparing the obtained RA deposition among the three administration protocols. The skin depositions of RA in stratum corneum and underlying skin were found to be lowest in the case of the treatment with free RA; conversely, significantly higher amounts of RA were accumulated in the case of the administration exploiting RA-loaded PDNPs. The authors also tested the RA delivery efficiency of mesoporous and solid RA-loaded PDNP formulations presenting two different diameters (500 and 300 nm), showing that the treatment with mesoporous nanostructures led to a higher RA skin accumulation compared to the administration through solid PDNPs. According to the findings of this study, solid and mesoporous PDNPs significantly improved the RA delivery into the stratum corneum and in deeper skin layers, highlighting moreover as the porosity and size of PDNPs influence the drug penetration across the skin [68].

PDNPs also represent an ideal platform for the design of smart organic stimuli-responsive drug delivery systems. The release of drugs associated with PDNPs can in fact be triggered by the exposure of polydopamine nanostructures to external stimuli such as NIR irradiation or acidic pH. For example, PDNPs were exploited to develop a stimuli-responsive anticancer carrier platform for the delivery of bortezomib (BTZ) [70]. In particular, PDNPs were functionalized with BTZ through the catechol groups of polydopamine with a pH-sensitive bond, and subsequentially decorated with glucosyl ligands targeting GLUT1, a protein over-expressed by tumor cells [70]. The BTZ release from the obtained polydopamine nanostructures was found to be 10–20% at pH 7.4, while reaching nearly 45–65% at pH 5.0 in the same time period (3 h). Moreover, a burst release of BTZ (90%) was observed after exposing the BTZ-loaded PDNPs to NIR irradiation at pH 5.0, most probably induced by the temperature increment caused by the photothermal mediated by PDNPs [70]. In another example, Fan *et al.* developed PDNPs loaded with doxorubicin and epigallocatechin-3-gallate and functionalized with folic acid for the potential treatment of breast cancer. In their study, the release of doxorubicin and epigallocatechin-3-gallate has been shown to be triggered by NIR irradiation and exposure to the acidic pH of intracellular compartments, like endosomes and lysosomes. Moreover, the authors reported the higher anticancer efficiency of the proposed nano formulation with respect to the treatment with free drugs, improving the survivability of breast cancer-bearing mice [71].

Another interesting example is provided by the study of Ren and colleagues, where mesoporous PDNPs loaded with doxorubicin and coated with platelet membranes were developed as anti-cancer therapeutic agents (Fig. 4) [72]. Doxorubicin-loaded PDNPs were able to target breast cancer cells in tumor-bearing mice thanks to the platelet membrane coating, outperforming the treatment with free doxorubicin in terms of drug delivery efficiency and therapeutic outcome. Moreover, once again the authors reported how the doxorubicin release from the PDNP carriers was enhanced by the irradiation of the nanostructures with NIR light and the exposure to acidic pH [72].

Besides delivery of chemotherapy drugs, relevant examples of polydopamine nanostructures for the treatment of other pathological conditions can be found in the literature.

Acter *et al.* proposed the development of photothermally responsive emulsions, composed of an oil core loaded with aspirin and stabilized by polydopamine nanobowls. The obtained Pickering emulsions showed the ability to release the loaded drug upon exposure to acidic pH or NIR irradiation [73]. Sun *et al.* developed hollow nanoparticles loaded with the peptide RL-QN15 for the treatment of skin wounds, demonstrating the ability of the obtained peptide-loaded nanostructures to outperform free RL-QN15 in terms of pro-healing potency on keranocytes, macrophages, mice model of skin wounds and skin scald, rat models of oral ulcers, and swine models of full-thickness injured wounds [74]. Park *et al.* developed hollow polydopamine nanoparticles functionalized with N-diazeniumdiolates acting as nitric oxide (NO) generators as

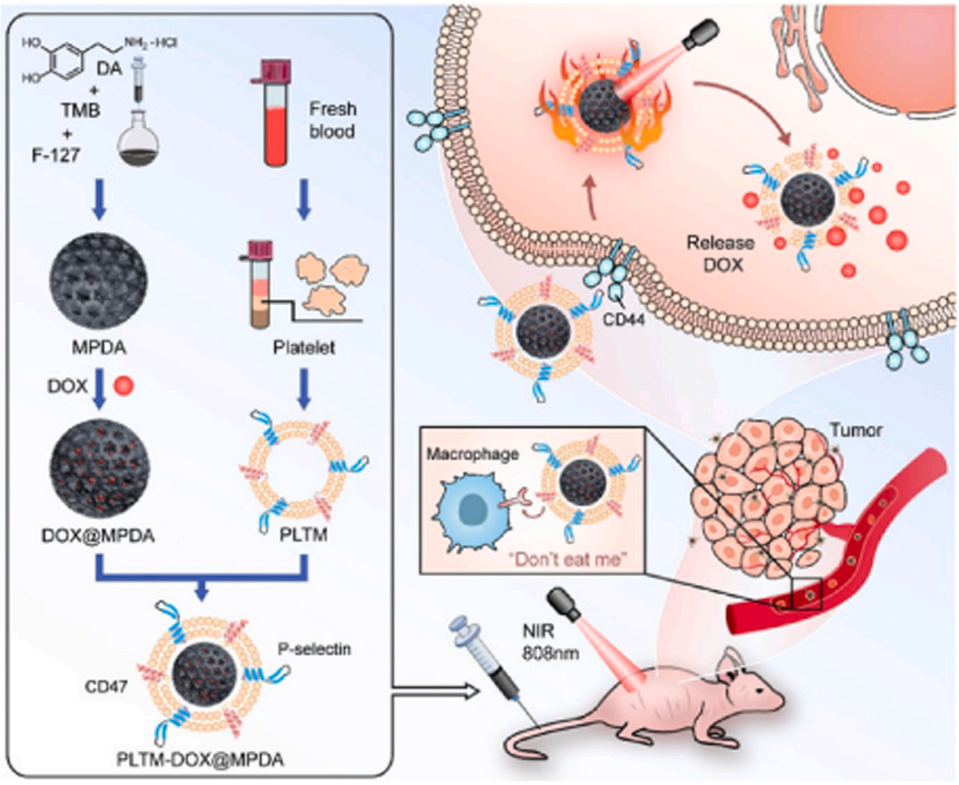

Fig. 4. Schematization of the development and testing of platelet membranes-coated and doxorubicin-loaded mesoporous PDNPs as multi-functional smart drug delivery systems for breast cancer treatment.
Reproduced with permission from Ref. [72].

antibacterial agents. The authors showed the ability of the obtained NO-generating hollow polydopamine nanoparticles to be highly biocompatible while eliciting an antibacterial effect upon *E. coli* and *P. aeruginosa* [75]. Lastly, Han *et al.* proposed mesoporous polydopamine nanoparticles loaded with prunetin and coated with hyaluronic acid as a potential treatment for UV-induced inflammation. The authors demonstrated the ability of the developed nanostructures to reach the skin inflammation site on in vivo mice model, leading to an accumulation of puretin and to consequent anti-inflammatory and antioxidant effects on skin cells [76].

Polydopamine nanostructures in photothermal therapy

NIR light-based stimulation has emerged as a powerful and versatile approach to generate highly localized temperature increments within tissues and biological structures. NIR light occupies a unique spectral window in the electromagnetic spectrum, with wavelengths ranging from 700 to 1400 nm [77]. This spectral range holds significance in biomedical research due to its ability to penetrate biological tissues with minimal absorption [78–80].

NIR-responsive nanostructures have been thus proven to be effective tools for PTT, a therapeutic strategy that allows the localized heat-induced treatment of tumors while minimizing damage to surrounding healthy tissue [81]. NIR-induced hyperthermia has the potential to induce apoptosis in cancer cells [82], and has been shown to enhance the sensitivity of cancer cells to chemotherapy [83] and ionizing radiation therapy [84]. Moreover, it has been demonstrated that the high metabolic activity and proliferative rate of cancer cells make them more sensitive to temperature increments with respect to their healthy counterparts [85,86].

Commonly plasmon resonant noble metal nanostructures such as gold nanoparticles have been the most widely exploited class of nanomaterials for PTT in past decades [10,87]. When metal nanomaterials are photoexcited with electromagnetic radiation at a specific wavelength, for instance within the NIR range, their valence electrons undergo coherent oscillations, named surface plasmon resonance, and consequently generate heat [88]. PDNPs, thanks to their previously mentioned photothermal conversion properties, represent a promising tool for the development of organic PTT nanoplatforms. This phenomenon has been associated to the light absorption of polydopamine in a wide range of wavelengths, from ultraviolet to NIR light; however, the precise molecular mechanism behind this phenomenon still remains poorly described [89]. Many studies have already demonstrated that PDNPs can achieve excellent results as NIR photothermal conversion agents, comparable to those obtained with traditional inorganic nanoparticles [90–92]. In a study conducted by our research group, we investigated the size-dependency of various PDNP properties using a library of eight nanoparticles with different sizes, ranging from 145 to 957 nm in diameter, demonstrating how larger nanostructures were able to perform as better NIR photothermal conversion agents compared to smaller ones [93].

In 2016, Wang *et al.* developed PDNPs functionalized with poly (ethylene glycol) (PEG) and loaded with doxorubicin and 7-ethyl-10-hydroxycamptothecin (SN38) as a multifunctional anticancer platform [94]. The anticancer efficiency of the obtained drug-loaded PEG-PDNPs was tested in vitro on PC9 lung carcinoma and MCF-7 breast cancer cells and in vivo on lung carcinoma-bearing bice [94]. The authors demonstrated the ability of these nanostructures to accumulate at the tumor site through passive targeting, and to release their molecular cargo in response to external stimuli like pH, ROS, and NIR irradiation (808 nm)

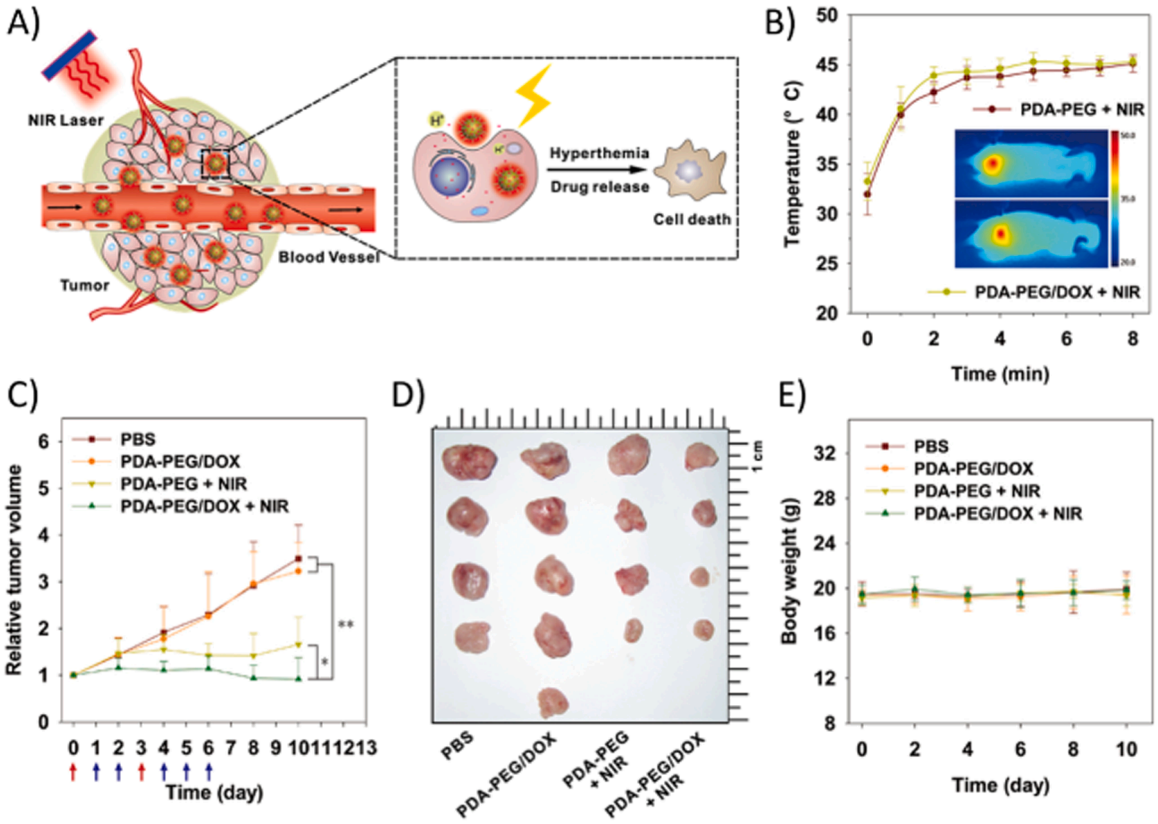

Fig. 5. Drug-loaded PDNPs as anticancer multifunctional platform. A) A scheme showing the NIR- and pH-triggered drug release from PDNPs and the synergistic treatment of the tumor; B) tumor-site temperature evolution of mice irradiated by NIR laser and treated with drug-loaded PDNPs; C) the tumor volume evolution in different experimental groups during the treatment period; D) overview of the excised tumors after the various treatment protocols; E) body weight trend of mice treated with and without drug-loaded PDNPs and NIR irradiation along the therapeutic period.
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[94]. Moreover, the authors reported how the treatment with drug-loaded PDNPs and NIR irradiation was able to induce cancer cell death and reduce tumor volume, outperforming the treatment with free drugs and plain nanostructures (Fig. 5) [94].

In 2018, Zhang *et al.* proposed PDNPs functionalized with a pH-sensitive camptothecin (CPT)-containing polymeric prodrug (PCPT) for the treatment of ovarian carcinoma [30]. PCPT-loaded PDNPs were tested as drug carriers and PTT platforms both in vitro on HeLa cells and in vivo on HeLa-bearing mice. The authors reported that the release of CPT from PDNPs could be triggered both by exposure to acidic pH and by the irradiation of the nanostructures with a NIR laser source (808 nm) [30]. Moreover, the authors demonstrated the synergic effect of PCPT and PDNPs-mediated PTT both in vitro and in vivo, where the combinatory treatment with PCPT-PDNPs and NIR irradiation was able to outperform the treatment with just plain PDNPs or free PCPT in terms of induction of cancer cell apoptosis and reduction of tumor volume [30].

PDNPs have also been exploited for the development of NIR-responsive hydrogels in the context of cancer treatment. Injectable self-healing hydrogels are smart soft materials able to repair any damage to their structure, and that can be exploited as drug carriers to achieve a sustained and localized release [95]. Wang *et al.* developed a thermo-sensitive self-healing gel exploiting the reaction between poly(ether-imide) (PEI) and the acetoacetate groups in the four-armed star-shaped poly(2-(dimethylamino)ethyl methacrylate-*co*-2-hydroxyethyl methacrylate) modified with tertbutyl acetoacetate (DMAEMA-co-HEMA-AA), loaded with PDNPs and doxorubicin [95]. The obtained PDNPs and doxorubicin-loaded hydrogels were then injected in breast cancer-bearing mice at the tumor site and exposed to NIR radiation. The NIR-induced photothermal conversion of PDNPs led to the shrinkage of the hydrogel with the consequent release of doxorubicin from its matrix. The combination of PTT, drug release, and physical stress induced by the hydrogel contraction was able to induce cancer cell death and reduction of the tumor volume [95].

An in vivo evaluation of PDNP NIR-induced hyperthermia for the ablation of central nervous system (CNS) cancers localized in deep brain tissue was performed by Liu and colleagues by analyzing PTT mediated by PDNPs injected in the hippocampus of rats [96]. After 30 min from the injection, the rat brain was exposed to NIR laser irradiation (808 nm) for 10 min, with a the temperature increment exceeding 60 °C after 6 min of irradiation, leading to a precise and localized ablation of deep brain tissues (the authors reported an ablated tissue volume of~6.5 mm^3) [96]. Moreover, PDNPs were found to not cause significant damages to brain tissues, with the exception of small scars or blood clots caused by the microinjection. PDNP NIR-mediated hyperthermia presented minimal to no damage to the non-irradiated brain tissues, demonstrating the feasibility of polydopamine nanostructures as PTT platforms in the context of CNS disorder treatment, and their potential suitability in place of other more harmful and less localized thermal ablation approaches, for example envisioning radiofrequency and focused ultrasound [97,98].

In an interesting study from 2022, Li *et al.* developed and compared the anticancer efficiency of solid and mesoporous doxorubicin-loaded and PEG-coated PDNPs [99]. In their study, they demonstrated that both nanostructures were able to act as stimuli-responsive drug carriers and NIR-PTT platforms inducing apoptosis in 4T1 cancer cells [99]. However, the authors reported how mesoporous PDNPs outperformed solid nanostructures in terms of drug loading and release efficiency, photothermal conversion abilities, and degradation speed [99].

PDNP-mediated PTT has also been used for other therapeutic purposes beyond cancer therapy. For example, in an in vivo study performed in 2021, Fang *et al.* exploited PDNPs as an effective thrombolytic treatment [100]. The authors developed PDNPs loaded with urokinase (UK) and functionalized with the Arg–Gly–Asp (RGD) peptide for the effective targeting and treatment of thrombosis. The functionalization with RGD allowed the PDNPs to target the thrombus site, while the guanidine group of L-arginine present in the peptide chain associated with the nanostructures permitted the ROS-induced production of NO. The NO produced by the nanostructures promoted the growth of vascular endothelial cells leading to the restoration of damaged blood vessels. Moreover, the NIR irradiation of the PDNPs was able to induce the ablation of the thrombus and further promote the growth of vascular endothelium cells owing to the pro-angiogenic effects of the released NO [100].

Acter *et al.* developed polydopamine nanobowls loaded with doxorubicin for combined drug delivery and PTT treatment of ovarian cancer; they demonstrated the ability of the developed nanoplatforms to be internalized by HeLa cancer cells, release the loaded doxorubicin, and act as PTT agents upon NIR irradiation inducing cancer cell death [101].

Polydopamine nanostructures in photodynamic therapy

PDNPs have been extensively studied as platforms for photodynamic therapy (PDT) in the treatment of various forms of cancer [102]. PDT is a non-invasive therapeutic approach based on the irradiation of specific molecules, called photosensitizers, with light at specific wavelengths. Photosensitizers, when irradiated, can pass from a ground molecular state to an excited (triplet) state and subsequentially release the accumulated energy to the oxygen molecules present in the surrounding environment [102,103]. This process can generate high levels of ROS such as singlet oxygen ($^1O_2$), that are highly toxic to cancer cells being able to cause damage to macromolecules and cellular structures.

Some of the most commonly used photosensitizers include chlorin e6 (Ce6) [104], porphyrin [105], and indocyanine green (ICG) [106,107]. The major problems related to the use of photosensitizers are their poor water stability and rapid blood clearance [102], and to overcome these limitations, PDNPs have been proposed as potential carriers. Similarly to what discussed in the context of the functionalization of PDNPs with drugs, photosensitizers can be associated with PDNPs through chemical conjugation by exploiting the high reactivity of polydopamine, through physical absorption strategies exploiting weak interactions, or through encapsulation procedures [102]. Usually, PDNPs loaded with photosensitizers are exploited in anticancer strategies combining PDT and PTT, due to the ROS generation ability of the loaded photosensitizers and the photothermal conversion properties of polydopamine [102].

Zhang *et al.* conjugated Ce6 on the surface of PDNPs through the reaction with 1-ethyl-3-(3-dimethylaminopropyl) (EDC) and N-hydroxysuccinimide (NHS); the developed PDNPs-Ce6 were tested as PDT/PTT combinatory platforms on mice bearing HepG2 liver cancer cells [108]. PDNPs-Ce6 showed the ability to generate ROS when irradiated with a laser at 670 nm, and to generate localized temperature increments when irradiated with an 808 nm laser. The combination of the two effects was able to induce cancer cell death and reduce the overall tumor volume in the xenograft animal model [108].

Poinard *et al.* developed PDNPs loaded with Ce6 through π-π stacking, enabling a controlled release of Ce6 from the polydopamine nanostructures [109]. PDNPs-Ce6 were tested on T24 carcinoma cells, showing the ability to act as a PDT/PTT platform when irradiated with a laser at 665 nm [103].

Still in the context of polydopamine nanostructures loaded with Ce6, Chen *et al.* proposed a different approach involving the development of bovine serum albumin (BSA) and polydopamine hybrid nanostructures [110]. In their study, the authors co-precipitated BSA with Ce6 obtaining Ce6 @BSA nanostructures, that were subsequentially coated with polydopamine leading to the formation of PDNPs-BSA-Ce6 hybrid nanostructures referred to as dual-mode therapeutic nanoparticles (CBP NPs). The obtained CBP NPs were tested on 4T1, MCF-7, HeLa, and MCF-10A cancer cells, and in mice bearing breast cancer cells, showing the ability to generate ROS when irradiated with a 660 nm laser and act as a PTT platform when irradiated with an 808 nm laser, demonstrating high anti-cancer efficiency in all the tested conditions (Fig. 6) [110].

As previously mentioned, ICG is another commonly used

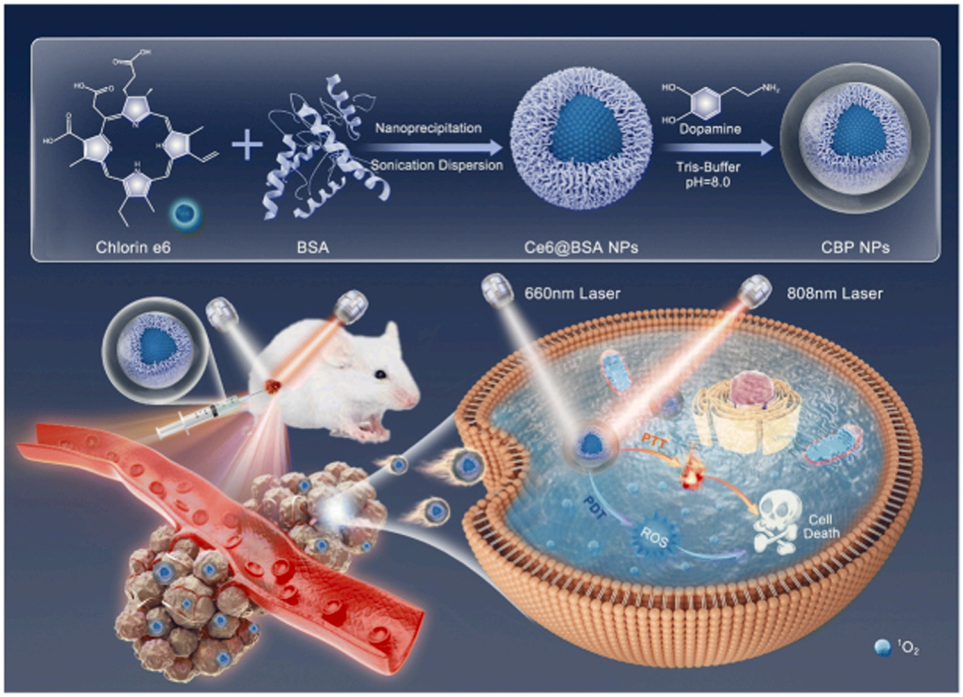

Fig. 6. Development of hybrid BSA polydopamine nanostructures loaded with Ce6 for combined PTT and PDT against cancer. Image reproduced with permission from Ref. [110].

photosensitizer exploited for the functionalization of PDNPs for PDT approaches. ICG is characterized by a light absorption peak at 780 nm and the ability to act as a PDT and PTT conversion agent, besides being a widely used fluorescent tracker in diagnostic applications [111]. Moreover, the NIR absorption of ICG makes it a more suitable candidate for PDT and imaging applications with respect to other photosensitizers, indeed because of the previously discussed high tissue penetrability of NIR irradiation. However, its use is limited by aggregation and low stability in water solution, quick clearance, and accumulation in off-target organs [112]. To overcome these limitations, Liu *et al.* developed hybrid nanostructures composed of hyaluronic acid loaded with ICG and coated with polydopamine [113]. The obtained nanostructures showed the ability to generate ROS and act as photothermal conversion agents when irradiated by NIR laser, thus being able to elicit anti-cancer effects both in vitro on 4T1 cells and in vivo in mice bearing breast cancer cells [113].

In another study, PDNPs were loaded with a new form of ICG (IR820) and tested as PDT/PTT platforms for the treatment of psoriasis [114]. The obtained PDNPs/IR820 were able to penetrate the psoriasiform skin of an imiquimod (IMQ)-stimulated murine model, and to act as ROS generators and cause temperature increments upon NIR laser irradiation, leading to the removal of the psoriasis plaque and relive psoriasis-induced inflammation [114].

Antioxidant properties of polydopamine nanostructures

The overproduction of ROS has been associated with the onset and progression of several health disorders, ranging from neurodegenerative diseases to various forms of cancer [115]. ROS are in fact able to induce damage to macromolecules and cellular components such as proteins, nucleic acid, cellular membranes, and mitochondria, leading to severe impairments of cellular functions [115]. Therefore, the research in the development and exploitation of antioxidant molecules as countermeasures for oxidative stress is a "hot" topic in nanomedicine: in this context, in fact, antioxidant nanoparticles have been recently proposed in the treatment of several pathologies [115]. Some of the most used classes of antioxidant nanostructures include manganese oxide [116], cerium oxide [117], and platinum [118] nanoparticles. Inorganic antioxidant nanostructures have been tested in the context of Parkinson's disease [119], Alzheimer's disease [120], ischemic stroke [121], metabolic disorders [122], senescence [123], treatment of various forms of cancer [124], and even, by our group, in space biology [125].

PDNPs, presenting excellent antioxidant properties, represent an ideal alternative to the just-mentioned inorganic nanostructures. The antioxidant properties of PDNPs have been linked to their catechol-, quinone-, and imine-rich surfaces, which grants them the ability to act as ROS scavengers against a vast variety of different free radicals. For example, Guo *et al.* in 2021 theorized that the polydopamine ability to scavenge alkyl peroxyl radicals ($^{\bullet}$ROOC, produced during autoxidation of lipid substrates induced by hydroperoxyl radicals, $^{\bullet}$HOOC) could be due to a H-atom transfer mechanism involving the free radical and the quinone groups of polydopamine [28].

In 2017, Shi and co-workers demonstrated the multiple enzyme-mimicking antioxidant activities of melanin nanoparticles (chemically analogous of PDNPs) for the treatment of ischemic reperfusion brain injury [126]. The authors demonstrated how PEGylated melanin nanoparticles (PEG-MeNPs) were able to scavenge various types of ROS including superoxide ($O_2^{\bullet-}$), hydroxyl ($^{\bullet}$OH), nitric oxide ($^{\bullet}$NO) and peroxynitrite ($ONOO^-$) radicals. The results obtained by Shi and colleagues suggested that PEG-MeNPs may effectively neutralize these radicals through a nitration and nitrosation mechanism involving the phenolic groups abundant in melanin structures. Moreover, the authors showed how PEG-MeNPs could react with H_2O_2, indicating their possible catalase-like activity [126]. Lastly, PEG-MeNPs were exploited as a protective antioxidant platform to prevent ischemic-stroke-induced damage, demonstrating their beneficial effects by reducing ROS accumulation and inflammation in an in vivo rat model of ischemic stroke [126].

In 2018, Bao *et al.* reported antioxidant PDNPs in the treatment of periodontal disease [127]. In their study, the authors exploited PDNPs for the prevention of ROS accumulation both in vitro on HGE cells and in vivo in a lipopolysaccharides (LPS)-induced animal model of periodontal disease [127]. They reported the antioxidant effect of PDNPs against $^{\bullet}O_2^-$ and $^{\bullet}$OH, their capacity to reduce ROS levels both in vitro

and in vivo, and the ability of polydopamine nanostructures to reduce the expression of inflammation-related markers such as tumor necrosis factor α and interleukin ß [127].

Jia *et al.* demonstrated the potential of PDNPs as protective antioxidant platforms for the prevention of irradiation-induced intestinal injury [128]. In their study, they tested PDNPs on mice models of total body irradiation. PDNPs showed a clear antioxidant activity against $O_2^{\bullet-}$ and $^{\bullet}OH$ radicals, two of the main ROS species involved in oxidative stress-induced cellular damages [128]. Moreover, the authors reported how PDNPs were able to prevent the depletion of intestinal stem cells, promote the repair of intestinal structures and activities, suppress intestinal cell apoptosis and pyroptosis, and alleviate DNA damage induced by ionizing radiation [128].

Our group previously reported the antioxidant properties of PDNPs both on neuron-like cells and on skin fibroblasts derived from patients affected by autosomal recessive spastic ataxia of Charlevoix-Saguenay, a rare neurological disease caused by congenital mitochondrial disorders [129,130]. In our studies, we were able to demonstrate the protective effects on both cellular models in terms of reduction of ROS levels in the presence of a pro-oxidative stimulus (*tert*-butyl hydroperoxide), and the prevention of ROS-induced mitochondrial impairments such as morphological aberrations and loss of membrane potential [129,130].

Zhang *et al.* proposed PDNPs as antioxidant and anti-inflammatory enhancers against UV-induced skin damage [131]. In their study, they exploited PDNPs for the development of anti-UV sunscreen, and tested the efficiency of this formulation on mice models of UV irradiation [131]. The formulation was able to prevent UV-induced damages on the skin of mice exposed to UV irradiation, being able to absorb UV, reduce ROS and inflammation, prevent UV-induced damages (epidermal hyperplasia, transepidermal water loss, and skin barrier disruption), and being able to counteract photoaging by maintaining the metabolism of collagen fibers and elastins [131].

PDNPs have also been studied in the context of neurodegenerative disorders [132]. For example, in 2023 Zhu *et al.* proposed PDNPs as a potential countermeasure for inflammatory depression [132]. PDNPs reduced oxidative stress in an LPS-induced animal model of inflammatory depression, being also able to limit the production of serum inflammatory cytokines, inhibit microglia activation, restore synaptic loss, and alleviate splenomegaly, thus improving the anxiety and depression of the treated animals [132]. Still in 2023, Han *et al.* proposed PDNPs as an anti-senescence treatment. In this study, ultra-small PDNPs (3 nm) were tested as an anti-age formulation on 293 T cells and on two in vivo models of senescence (D-galactose-induced *Drosophila melanogaster* and doxorubicin-induced mouse model) [29]. The authors reported the ability of the developed PDNPs to counteract the accumulation of various forms of ROS, exert cytoprotective effects against oxidative stress-induced damages, restore senescence-impaired functions in mice (renal activity, tissue homeostasis, fur density, and motor ability), and prolong the life span of the *Drosophila* senescence model [29].

Polydopamine nanostructures as smart modulators of cellular activities

One of the most exciting applications of smart nanomaterials is represented by the possibility of remotely stimulating cellular activities in a non-disruptive, non-invasive, and highly localized manner. Some examples include the modulation of neuronal cell activation or the remote control of stem cell differentiation by exploiting piezoelectric nanoparticles [6,133]. Moreover, the literature has extensively documented how heat stimuli within physiological ranges can effectively modulate various cellular behaviors, including gene expression [134], stem cell differentiation [135], and neuron activation [136]. In this context, the application of photothermal stimulation exploiting NIR radiation stands out as a powerful tool for remotely manipulating cell activities and maturation [137]. This technology holds great promise for advancing our understanding of cellular processes and developing innovative therapies for the treatment of various health disorders. NIR-responsive gold nanostructures have been exploited for the non-disruptive remote control of cellular activities such as the remote control of muscle cell contraction [138], modulation of gene expression [139,140], and the induction of neural activation [141,142]. However, as we extensively discussed in the previous Sections, the use of noble metal in biomedicine is limited by their potential toxicity and their lack of biodegradability.

In this view, polydopamine nanostructures are a suitable organic platform for the remote modulation of cellular activities, due to their previously discussed photothermal conversion properties. For example, in a recent study, Li *et al.* designed PDNPs loaded with CpG oligodeoxynucleotides (CpG ODNs), an immunostimulatory nucleic acid adjuvant able to induce the maturation of dendritic cells (DCs), and thus to stimulate antitumor immune responses [143]. Conventional PTT approaches have the potential to induce immunogenic cell death, which can lead to the release of tumor-associated antigens and the recruitment of DCs [144–146]. However, a disruptive PTT is usually unable to provide a sufficient activation signal to DCs, and as a result, the immune system ability to inhibit tumor recurrence and proliferation may be inadequate, eventually leading to tumor recurrence [147]. The combination of the NIR irradiation with CpG ODNs resulted in a significant synergistic treatment in a mouse model of melanoma. This combined therapy enhanced the maturation of DCs and the activation of T cells with respect to PTT or CpG ODNs individually. Moreover, this approach addressed the issue of insufficient immune response at distant tumor sites, a limitation observed with PTT alone, besides alleviating the immunosuppressive environment within the tumor [143].

PDNP photothermal conversion showed interesting applications also in the context of cell transfection and gene therapy. For example, Zhang *et al.* exploited PDNPs for the transfection of cancer cells both in vitro (HepG2 cells) and in vivo in KB tumor-bearing mice [148]. In particular, the authors exploited PDNPs loaded with p53 DNA as a gene delivery platform. PDNP transfection efficiency was compared to commercial lipofectamine 2000, obtaining similar transfection efficiency but with lower cytotoxicity. Moreover, the application of NIR stimulation increased by 4.5 times the transfection level of p53, thanks to the quick escape of gene complexes from the endosomes. The synergistic efficacy of gene/PTT resulted in an almost completed depletion of the tumor mass in treated mice after only one intratumoral injection, and in a tumor inhibition efficacy of 99% [148].

Intracellular temperature increments in neuronal cells are known to cause the stimulation of nerve transient receptor potential (TRP) channels, leading to membrane depolarization and neuronal activation [149]. In a study performed by our group, we showed the ability of PDNPs to act as an organic NIR-responsive platform for the modulation of neuronal activities. We were able to demonstrate that PDNPs can be used to finely tune the intracellular temperature of neuronal-like cells in a non-disruptive and non-cytotoxic manner, with a consequent increment of the intracellular calcium concentration, suggesting neuronal activation [129]. In 2021, Derami *et al.* showed the possibility of PDNPs to exert a reversible modulation of the electrical activity of neurons and cardiomyocytes, thanks to NIR irradiation [150]. PDNPs have been exploited to modulate neuronal activity and cardiomyocyte beating frequency. By calibrating NIR laser power and stimulus duration, the authors demonstrated the possibility of modulating the electrical activities of hippocampal neurons and of suppressing or enhancing the beating rate of induced pluripotent stem cells-derived cardiomyocytes, demonstrating the potential of polydopamine nanostructures as a minimally invasive photothermal transducer [150].

Polydopamine nanostructures in imaging applications: Towards organic contrast agents

As mentioned, a theranostic smart nanoplatform combines a therapeutic effect with a diagnostic action, being thus generally able to be

imaged and localized inside tissues and cells and to provide information about its surrounding biological environment [1]. Several approaches have been proposed to visualize PDNPs inside living organisms; for example, polydopamine nanostructures have been conjugated with MRI inorganic contrast agents such as Gd [151], iron oxide nanoparticles [152], manganese oxide [153], and nickel [154]. PDNPs have been also radiolabeled with ^{131}I for SPECT imaging [155] or functionalized with noble metal as gold nanoparticles for Raman spectroscopy analysis [156]. Despite the potential of these nanostructures, we would like to drive our attention on studies exploiting completely organic formulations, thus avoiding the already mentioned drawbacks of inorganic nanoparticles [157,158].

The visualization of completely organic PDNP formulations within biological structures can be achieved mainly by means of fluorescence imaging and PA analysis. The fluorescence-based imaging of PDNPs is usually achieved through the functionalization of polydopamine with fluorescent moieties either through Michael addition, encapsulation, or weak molecular interactions [102]. PDNPs have been easily functionalized with a vast variety of fluorescent tracers such as carbocyanine dyes, rhodamine, cyanines, and fluorescein, enabling their visualization through fluorescence microscopy in vitro and in vivo [159]. Previously discussed photosensitizers, Ce6, IR820, and ICG, can also be used as fluorescent tracers in addition to their ability to act as PDT/PTT platforms [111,160,161]. One notable example of a fluorescent tracer is also represented by doxorubicin that, owing to its fluorescence properties, can enable the direct imaging of doxorubicin-loaded PDNPs [162].

The use of fluorescent tracers for the visualization of PDNPs is however limited by several issues, including as the fluorescence quenching effect of polydopamine and the pH-dependent detachment of the fluorescent molecule from the nanostructures [163]. PA imaging has gained attention in recent years as a label-free imaging technique for diagnostic purposes [164]. PA imaging is based on the PA effect generated by endogenous chromophores or exogenous contrast agents when irradiated with an external laser source: briefly, when the chromophores or the PA contrast agents are irradiated with a proper laser source, they can absorb part of the irradiation and undergo a rapid thermoelastic expansion [164]. The mechanical expansion of the photo-absorber is then able to generate a wide-band ultrasound wave that can be detected by a transducer and converted to electric signals that are then processed to form an image [164]. Commonly noble metal nanostructures such as gold [164] and silver [165], carbon nanotubes [166], and dyes like ICG [167] and methylene blue [168] are the most widely used contrast agents for PA imaging.

Several works however reported also the potential of PDNPs as PA contrast agents. For example, Li *et al.* developed PDNPs modified with the arginine-glycine-aspartic-cysteine acid (RGDC) peptide and loaded with doxorubicin for the treatment and PA imaging of cervical cancer both in vitro and in vivo. The obtained nanostructures, characterized by a high targeting and anti-cancer efficiency, showed the ability to act as PA contrast agents enabling the localization of the PDNPs and the tumor imaging even at concentrations as low as 15 μg/ml [169]. In another example, Fu *et al.* compared the PA and PTT properties of PDNPs obtained through solution oxidation and of melanin nanostructures developed through bacteria-mediated synthesis [170]. The authors showed that the bacteria-derived melanin nanostructures outperformed the PDNPs obtained through solution synthesis in terms of both PA signal and PTT effects in 4T1 tumor-bearing mice [170].

In another study, hyaluronic acid-coated PDNPs (HA-PDNPs) were exploited for the PA-guided imaging of endometriosis (EM) lesions in vivo, as an innovative tool for the diagnosis and monitoring of this disease [31]. The obtained HA-PDNPs showed the ability to accumulate at the boundary of EM lesions in mice models. Moreover, PDNP-based volumetric reconstruction obtained through PA imaging accurately assessed EM progress [31]. Zhuang and colleagues developed a rather interesting PDNP theranostic formulation based on polydopamine hollow nanocapsules (PDAC) loaded with doxorubicin through electrostatic interaction and π-π stacking [171]. The obtained doxorubicin-loaded PDAC showed the ability to act as an excellent PA contrast agent outperforming solid PDNPs of the same size (approximately 200 nm) both in vitro and in vivo [171]. Moreover, these nanocomplexes showed high anticancer efficiency upon NIR irradiation both in vitro and in mice bearing breast cancer cells, outperforming the treatment with free doxorubicin. It is worth mentioning that, like in the case of the examples discussed in the previous Sections, even in this case the authors observed a burst release of doxorubicin from the PDAC caused by NIR irradiation and exposure to acidic pH [171].

PDNPs have also been used in combination with other PA contrasts agent to improve their overall PA signal. For example, Yim *et al.* developed PDAC loaded with different PA molecular contrast agents like Nile blue and methylene blue for the direct detection of heparin in the whole human blood [172]. The obtained dye-loaded PDAC showed a PA signal higher than the free dyes and enabled the direct detection of heparin; moreover, the authors showed that the obtained PA signal of dye-loaded PDAC from the blood of 17 patients linearly correlated with the heparin values obtained through other conventional methods like clotting time [172]. As a last very recent example, Ren and colleagues developed a multifunctional polydopamine nanocomposite combining most of the polydopamine properties that we discussed in this review. The developed nanostructures were composed of mesoporous PDNPs loaded with the photosensitizer IR780, the natural NO donor L-arginine, and functionalized with BSA [173]. The obtained polydopamine nanocomposites showed the ability to act as PDT and PTT platforms, PA contrast agents, and NO generators upon NIR irradiation [173]. The synergic combination of these effects enabled the detection of tumors in osteosarcoma-bearing mice, and an overall anti-cancer efficiency far superior than that one of the single plain treatments (Fig. 7) [173].

Conclusions: Current limitations and future perspectives

As discussed in this review, PDNPs have been studied for various applications including drug delivery, PTT, PDT, antioxidant-based therapies, remote stimulation of cellular functions, and imaging of biological structures (a summary of the articles discussed in this review can be found in Table 1).

To the best of our knowledge, despite the promising properties of polydopamine nanostructures, no clinical trials employing PDNPs are ongoing. In our opinion, several key points currently limit the applicability of PDNPs in human healthcare, as discussed in the following.

1) The precise molecular mechanism behind polydopamine formation, as we previously discussed, remains largely unknown, opening potential concerns for their applications [36]. For example, despite the synthesis of polydopamine does not usually involve the use of organic solvents or other toxic compounds, the presence of non-polymerized dopamine molecules in PDNP dispersions could potentially lead to adverse effects [36]. Moreover, as described, even the overall molecular structure of polydopamine itself is still largely unknown [174]: the analysis of PDNP formation mechanism and the development of new models that describe their molecular composition are thus pivotal points to be addressed before a successful implementation of polydopamine nanostructures in clinical applications.
2) The properties of PDNPs in terms of antioxidant capacity, photothermal conversion abilities, drug loading efficiency, and overall interaction with tissues and cells are highly dependent on the nanostructure characteristics such as diameter, porosity, and shape [24,68]. Currently, there is an evident lack of standardization among the studies exploiting PDNPs for biomedical applications, with polydopamine nanostructures of various sizes, shapes, surface chemistry, and molecular cargo being investigated as countermeasures for various health disorders ranging from cancer therapy [52,175] to the treatment of neurodegenerative diseases [132]. To maximize the

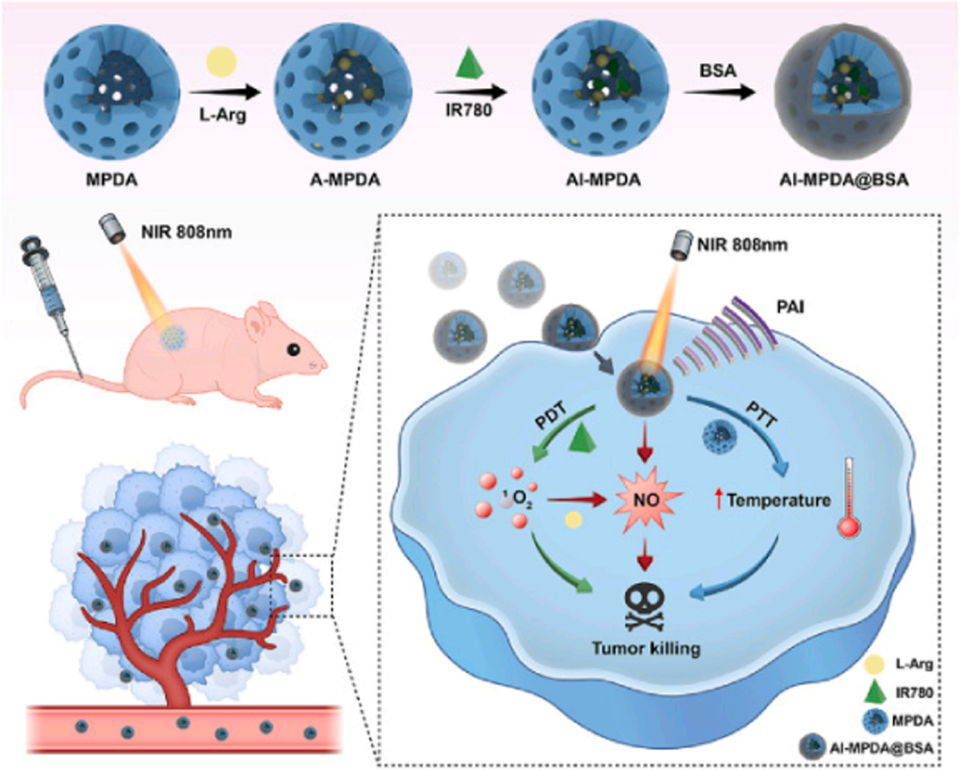

Fig. 7. Mesoporous PDNPs loaded with L-arginine, IR780, and functionalized with BSA are able to act as a theranostic platform for PDT, PTT, PA imaging, and NO generation upon NIR irradiation, enabling the visualization and treatment of osteosarcoma.
Image reproduced with permissions from Ref. [173].

therapeutic efficiency of PDNPs and facilitate their transition into clinical applications, a set of highly standardized and reproducible fabrication procedures should be developed, investigated, and implemented.

3) The high reactivity of PDNPs represents a double-edged sword, since from one side it grants the possibility to easily functionalize PDNPs with a vast variety of molecules [59], but it could also potentially lead to unexpected interaction with biological structures. As it has been extensively described in the literature, when nanostructures come in contact with biological fluids they are almost immediately coated with biological molecules such as proteins, lipids, and nucleic acids, collectively referred to as "biomolecular corona" [176]. This phenomenon could be exacerbated by the previously described high reactivity of polydopamine, leading to the formation of a biomolecular corona associated with PDNPs that could potentially cause unexpected interactions with tissues and cells and compromise PDNP properties or their colloidal stability. To date, there is no extensive analysis of the formation of biomolecular corona associated with PDNPs when exposed to biological environments, and neither of the potential strategies to prevent or at least reduce the corona formation. An extensive analysis of this phenomenon for the future clinical application of polydopamine nanostructures is needed, in particular in terms of parameters (size, porosity, shape, surface functionalization) potentially affecting biomolecular corona. Moreover, strategies to prevent the opsonization of PDNPs need to be developed and investigated, including the coating of polydopamine nanostructures with protective molecules such as PEG.
4) The overall degradation process of PDNPs and polydopamine in general is still under investigation. It is known that external parameters such as pH and exposure to ROS can affect the overall degradation of PDNPs over time; however, both the molecular mechanism behind this process and the products of PDNP degradation are largely unknown [20,24,35], and PDNP degradation products could potentially lead to unexpected biological outcomes or even adverse health effects. Therefore, there is a need to extensively investigate the biodegradation process of PDNP with particular attention to their degradation products.
5) Literature studies focused on the analysis of the long-term effects of PDNPs in living animals are still fairly limited, with most articles focusing on in vitro tests or reporting in vivo short-term analysis [19,20]. For a successful implementation of PDNPs in clinical applications, the study of the effects of chronic exposure to polydopamine nanostructures using in vivo models is a pivotal necessity.
6) Most studies currently present in the literature describes the synthesis of PDNPs in relatively small quantities (commonly with a PDNP yield in the order of hundreds of milligrams) [177]. The scalability of the PDNP synthesis procedure and the large-scale production of polydopamine nanostructures is an essential point for their exploitation in clinical applications. As discussed, the yield of PDNP synthesis can be affected by several parameters such as the reaction pH, the dopamine concentration, and the process temperature [40,41]. A potential solution for the large-scale production of PDNPs could be the development of batch reactors able to produce polydopamine nanostructures in large quantities. Flow reactors are for example commonly exploited for the fabrication of inorganic nanostructures like SPIONs or silica nanoparticles [178,179]. A major obstacle to the large-scale production of PDNPs is represented by the relatively slow kinetics of the polydopamine synthesis reaction [19]. Several strategies could be exploited to overcome this limitation; for example, it has been demonstrated that the application of external stimuli such as microwave [180] or UV irradiation [181] can affect the formation speed of polydopamine films. A similar approach could be exploited to improve the kinetics of PDNP formation facilitating the large-scale production of polydopamine nanostructures.

Table 1
An overview of the studies discussed in this review showing the exploited nanostructure composition, along with their main features.

Reference	Nanostructures	Loaded molecules / functionalization	Loading / encapsulation data	Size	Application
[67]	PDNPs	Loaded with gambogenic acid and functionalized with folic acid and sodium alginate	Encapsulation efficiency about 86%	185.3 ± 5.1 nm	Delivery of gambogenic acid as a treatment for breast cancer
[68]	Mesoporous and solid PDNPs	Loaded with RA	Encapsulation efficiency about 90%	500 nm and 300 nm	Delivery of RA to skin
[70]	PDNPs	Loaded with BTZ and functionalized with glucosyl ligands	Loading efficiency up to 11 wt%	150-200 nm	Delivery of BTZ as a treatment for breast cancer
[71]	PDNPs	Loaded with doxorubicin and epigallocatechin-3-gallate and functionalized with folic acid	Encapsulation efficiency up to 93%	436.77 ± 25.31 nm	Delivery of doxorubicin and epigallocatechin-3-gallate as a treatment for breast cancer
[72]	Mesoporous PDNPs	Loaded with doxorubicin and functionalized with platelet membranes	Loading efficiency 38 wt%; Encapsulation efficiency 98%	184 nm	Delivery of doxorubicin as a treatment for breast cancer
[73]	Oil emulsion stabilized by polydopamine nanobowls	Oil emulsion loaded with aspirin	N/A	180 nm	Developing of a smart drug-delivery system
[74]	Hollow PDNPs	Loaded with the peptide RL-QN15	Approximately 80% encapsulation efficiency	52 nm	Treatment of skin wounds
[75]	Hollow PDNPs	Functionalized with N -diazeniumdiolates	Up to 297 pmol of NO release *per* mg of PDNPs	45 nm	Antibacterial action through NO generation
[76]	PDNPs	Loaded with prunetin and functionalized with hyaluronic acid	N/A	Approximately 200 nm	Treatment of UV-induced inflammation
[94]	PDNPs	Loaded with doxorubicin and 7-ethyl-10-hydroxycamptothecin (SN38) and functionalized with PEG	Loading efficiency of approximately 33 wt% for DOX and approximately 11 wt% for SN38	98 nm	Delivery of doxorubicin and 7-ethyl-10-hydroxycamptothecin (SN38) and NIR-induced PTT as a treatment for lung carcinoma and breast cancer
[30]	PDNPs	Functionalized with PCPT	N/A	114	Delivery of PCPT and NIR-induced PTT for cancer therapy
[95]	Thermo-responsive hydrogels (DMAEMA-co-HEMA-AA) loaded with PDNPs	Loaded with doxorubicin	N/A	220 nm (PDNP size)	Development of injectable thermoresponsive hydrogels for the delivery of doxorubicin as a treatment for breast cancer
[96]	PDNPs	N/A	N/A	145 nm	Analysis of the potential of PDNPs as PTT platforms for the thermal ablation of deep brain tissues
[99]	Solid and mesoporous PDNPs	Loaded with doxorubicin and functionalized with PEG	Up to approximately 80% encapsulation efficiency	160 nm	Delivery of doxorubicin and NIR-induced PTT as a treatment for breast cancer
[100]	PDNPs	Loaded with UK and functionalized with RGD	RGD decoration 0.16 wt%	243 nm	PTT and NIR-induced NO-generation as a treatment of thrombosis
[101]	Mesoporous polydopamine nanobowls	Loaded with DOX	Loading efficiency 30 wt%	180 nm	PTT and DOX delivery as a treatment of ovarian cancer
[108]	PDNPs	Functionalized with Ce6	N/A	43 nm	PDT/PTT as a treatment for liver cancer
[109]	PDNPs	Loaded with Ce6	14.2 μM of Ce6 loaded in 1 nM PDNPs	260 nm	PDT/PTT as a treatment for urinary bladder cancer
[110]	Hybrid BSA/PDNPs	Loaded with Ce6	N/A	80.7 ± 6.6 nm	PDT/PTT as a treatment for various forms of cancer (breast, lung, and ovarian cancer)
[113]	PDNPs	Loaded with ICG and functionalized with hyaluronic acid	Up to 8.6% loading efficiency	318 nm	PDT/PTT as a treatment for breast cancer
[114]	PDNPs	Loaded with IR820	Encapsulation efficiency up to 97%	200 nm	PDT/PTT as a treatment for psoriasis
[126]	Melanin nanoparticles	Functionalized with PEG	N/A	120 nm	Antioxidant treatment against ischemic stroke
[127]	PDNPs	N/A	N/A	160 nm	Antioxidant treatment of periodontal disease
[128]	PDNPs	N/A	N/A	Diameter ranging from 107 to 183 nm	Antioxidant treatment of irradiation-induced intestinal injury
[129]	PDNPs	Functionalized with DSPE-PEG	N/A	200 nm	Antioxidant protection of neuronal-like cells and NIR-induced stimulation of neuronal activity
[130]	PDNPs	N/A	N/A	200 nm	Antioxidant treatment of ARSACS
[131]	PDNPs	N/A	N/A	119.4 nm	Development of PDNPs-based antioxidant sunscreen against UV-induced damage
[132]	PDNPs	N/A	N/A	250 nm	Antioxidant treatment of inflammatory depression
[29]	Ultrasmall PDNPs	N/A	N/A	3 nm	Antioxidant treatment of senescence
[143]	PDNPs	Loaded with CpG ODNs	N/A	70-90 nm	Modulation of DCs maturation as anti-cancer treatment

(*continued on next page*)

Table 1 (*continued*)

Reference	Nanostructures	Loaded molecules / functionalization	Loading / encapsulation data	Size	Application
[148]	PDNPs	Loaded with p53 DNA	N/A	320 nm	Gene delivery and PTT in the context of liver cancer treatment
[150]	PDNPs	N/A	N/A	465 nm	NIR-induced modulation of neuronal activation and cardiomyocytes beating frequency
[169]	PDNPs	Modified with RGDC and loaded with doxorubicin	Up to 2 wt% loading efficiency	120 nm	PA imaging and combinatory treatment of cervical cancer
[170]	PDNPs and melanin nanoparticles	N/A	N/A	200 nm (PDNPs); 40 nm (melanin nanoparticles)	PA imaging and PTT as a treatment of breast cancer
[31]	PDNPs	Coated with hyaluronic acid	N/A	200 nm	PA imaging of endometriosis
[171]	Hollow PDNPs	Loaded with doxorubicin	Up to 50% of loading efficiency	200 nm	PA imaging and combinatory treatment of breast cancer
[172]	PDNPs	Loaded with various PA contrast agents like Nile blue and methylene blue	Loading efficiency up to 81%	From 70 to 120 nm	Detection of heparin
[173]	PDNPs	Loaded with IR780, L-arginine, and functionalized with BSA	L-Arg loading content of approximately 11 wt%	180 nm	PA imaging, NO generation, and PDT/PTT as a treatment for osteosarcoma

In conclusion, PDNPs can be exploited for the development of organic multifunctional nanoplatforms able to tackle various health disorders. Owing to their widely discussed "smart" and theranostic features, PDNPs represent in our opinion one of the most promising classes of nanomedical products that, upon successful accomplishment of the previously described issues, could indeed become a protagonist of the near-future clinical practice.

CRediT authorship contribution statement

Battaglini Matteo: Conceptualization, Methodology, Writing – original draft. **Ciofani Gianni:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Carmignani Alessio:** Methodology, Writing – original draft. **Emanet Melis:** Conceptualization, Methodology, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

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

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Matteo Battaglini received his Ph.D. in biorobotics in 2020 from the *Scuola Superiore Sant'Anna* (Pisa, Italy) working on the synthesis and testing of nanomaterials for biomedical applications, besides the establishment of advanced in vitro models. He is currently a post-doctoral fellow working in the Smart Bio-Interfaces Research Line of the Italian Institute of Technology (Pontedera, Italy). His research interests include the design, fabrication, and testing of smart nanomaterials for human healthcare, and the development of innovative in vitro models of biological structures.

Melis Emanet obtained her Ph.D. (with honors) in biotechnology (Yeditepe University, Istanbul, Turkey) in 2019, carrying out research on ceramic nanomaterials as theranostic agents for cancer treatment. She is a postdoctoral fellow at the Italian Institute of Technology, Smart Bio-Interfaces Research Line, where she is performing research on smart drug delivery systems against liver cancer, supported by a fellowship from the Italian Association for Cancer Research (AIRC).

Alessio Carmignani successfully received his Ph.D. (with honors) in Biorobotics from Scuola Superiore Sant'Anna (Pisa, Italy) in 2023. His doctoral research focused on exploring and applying polydopamine nanoparticles for biomedical applications. His investigations ranged from harnessing the antioxidant capabilities of these nanoparticles for treating neurodegenerative diseases to creating responsive nanoplatforms for addressing colorectal cancer. He is now a research fellow at the Italian Institute of Technology, in the Smart Bio-Interfaces research line.

Gianni Ciofani, Ph.D., is Research Director at the Italian Institute of Technology, where he is Principal Investigator of the Smart Bio-Interfaces Research Line and Coordinator of the Center for Materials Interfaces (Pontedera, Italy). His main research interests concern smart nanomaterials for nanomedicine, complex in vitro models, and nanomedicine in altered gravity conditions. He author of about 180 papers on international journals, and coordinator or unit leader of several projects: in particular, he was awarded a European Research Council (ERC) Starting Grant and two ERC Proof-of-Concept Grant in 2016, 2018, and 2022, respectively. Thanks to grants from the Italian Space Agency and the European Space Agency, he had the opportunity to carry out experiments onboard the International Space Station in 2017, 2019, and 2022.