

Exploring and Anticipating the Applications of Organic Room-Temperature Phosphorescent Materials in Biomedicine and Dentistry

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Abstract: As popular materials, organic room-temperature phosphorescent (RTP) materials have been studied and developed in many fields. RTP materials have the characteristics of a high signal-to-noise ratio (SNR) and high reactive oxygen species (ROS) quantum yield, which can achieve clear bioimaging and efficient ability of anti-tumor and antibacterial, and have received extensive attention from researchers for imaging, tumor therapy, and antibacterial treatment. Moreover, owing to their flexible molecular structures and various synthesis systems and methods, it may be possible to design and synthesize materials according to individual physiologic environments of patients in medical applications, making bioimaging more accurate and greatly improving tumor and bacterial killing rates. So they have great development potential in the medical field. On the basis of introducing the mechanism of RTP materials that emit phosphorescence and generate ROS, this review summarizes the medical applications of RTP materials from three aspects—bioimaging, tumor treatment and antibacterial treatment—to provide a basis for their application in the field of stomatology.

Keywords: RTP materials, bioimaging, anti-tumor, antibacterial, ROS

Introduction

Bioimaging, tumor therapy and antimicrobial therapy are three important and correlated areas of medical development. Conventional bioimaging commonly utilizes inorganic materials containing Au,^{1,2} Ir (III),³ Fe₂O₃⁴ and other metallic materials as probes, which also has the ability of killing tumors. Although the materials can achieve targeted bioimaging of tumors in the body, they have the shortcomings of low tumor clearance rate and high toxicity,⁵ which cannot achieve tumor therapy. Therefore, people turn their attention to organic materials, such as diamond,⁶ graphene,⁵ carbon dots,^{7,8} which, due to their low toxicity, have been investigated extensively. However, current studies have shown that these materials have not yet led to the removal of tumors and bacteria, thereby limiting their application. Zhang et al prepared a carbon dot-embedded epitope imprinted polymer (C-MIP), and achieved targeted bioimaging of EGFR-overexpressing tumors in tumor-bearing mice by the specific recognition ability for the epidermal growth factor receptor (EGFR) of the material. However, C-MIP can only possess the capacity as a drug carrier and lacks the ability to eliminate tumor cells. In contrast, RTP materials possess dual bioimaging capabilities for both tumor and bacteria,⁹ as well as dual therapeutic abilities for anti-tumor and antibacterial treatments.^{10,11} At the same time, its side effects on the body are comparable to those of other organic materials, and it has a more comprehensive clinical application potential.

RTP materials are a class of materials that can sense, store, analyze, and respond to the surrounding environment or information.¹² Room temperature phosphorescent materials emerged in the 20th century. However, due to technical limitations, RTP materials are mainly derived from polymers such as proteins and aromatic compounds.^{13–15} Therefore,

there are problems such as difficult detection of phosphorescence and short emission time,¹⁶ which limit application of RTP materials to detection of protein structure and drug concentration by phosphorescence emission.¹⁷ With the development of various disciplines such as chemistry and physics, as well as advancements in nanomaterials technology, the synthesis methods of RTP materials have been continuously improved, and the material structure has been continuously optimized and combined with nanotechnology, so that RTP materials have a long emission life and high exciton utilization rate, which has attracted the attention of researchers in the fields of electronic information,¹⁸ optics^{19,20} and medicine.

RTP materials include a variety of materials with different properties, which are mainly divided into four types: inorganic compounds, organic-inorganic hybrid compounds, pure organic crystalline compounds and polymer compounds.²¹ Inorganic materials and hybrid materials generally contain metals such as silver and chromium, which have the disadvantages of high toxicity, high cost and complex synthesis process;²² polymer materials have the disadvantages of limited types of phosphors and limited topological structure of matrix materials,²³ which have great limitations in future application and development. In contrast, RTP materials have great advantages in the application and development of bioimaging, tumor therapy and antibacterial fields due to their low toxicity, diverse structures, especially their high SNR and high ROS yield. In recent years, researchers have successfully achieved efficient room-temperature phosphorescence emission and ROS generation by regulating the structures and composition of RTP materials. Currently, the reported RTP materials have a variety of structures, such as carbazole,²⁴ phenothiazine,²⁵ phenylpyrrole,²⁶ polycyclic aromatic hydrocarbon,²⁷ triphenylamine,²⁸ boron difluoride β -diketone,²⁹ naphthalimide and chromone derivative structures,^{30–32} which paves the way for enhancing properties and biomedical applications of RTP materials. (Figure 1)

However, due to the poor stability and poor tissue penetration of RTP materials, there may be some problems in the clinical application of stomatology, such as the unclear imaging of deep oral tumors and low tumor cell clearance rate because of poor tissue penetration and material decomposition which are caused by oral saliva PH, lysozyme content and other factors. Room-temperature phosphorescent (RTP) materials have long emission lifetimes and high exciton utilization and have attracted much attention in the fields of bioimaging,³³ tumor treatment and antibacterial treatment. However, RTP materials are still in the stage of clinical research and development, and applications in the diagnosis and treatment of diseases in the field of stomatology are relatively rare. Therefore, this review summarizes the principles

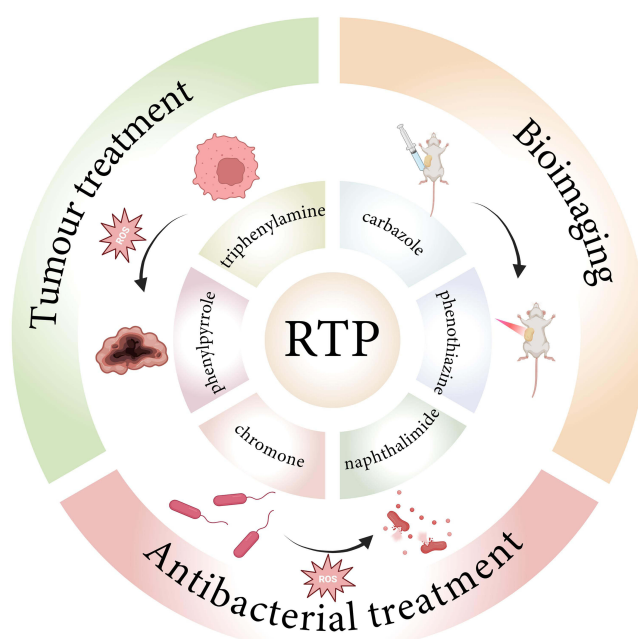


Figure 1 The applications of RTP materials and related structures.

Notes: Created in BioRender. Zhang, y. (2024) <https://BioRender.com/g40o406>

and research progress in RTP materials for use in bioimaging, tumor treatment and antibacterial treatment, and discusses their potential and problems regarding diagnosis and treatment in fields related to stomatology.

Mechanism

Unlike traditional fluorescence signals, RTP originates from the slow radiative transition of triplet excitons after excitation is stopped; thus, RTP has the unique characteristics of a longer lifetime and a greater Stokes shift.³⁴ The Jablonski diagram indicates that after RTP molecules absorb light energy, their electrons transition from the ground state (S0) to the singlet excited state (Sn).^{35,36} Next, the electrons have two main radiative transition paths. One involves vibrational relaxation (VR) or internal conversion (IC) from the singlet excited state (Sn) to the lowest singlet excited state (S1),^{37–39} followed by the emission of a photon upon the transition to the ground state (S0) and thus the generation of phosphorescence;^{40,41} the other path involves the intersystem crossing (ISC) transition from S1 to the triplet excited state (Tn) and then a transition from Tn to the lowest triplet excited state (T1) with the emission of a photon, resulting in phosphorescence.^{42,43}

Based on the two phosphorescence paths, there are two mechanisms for generating ROS. In the first type of mechanism, electrons are channelled from the Sn intersystem to T1 to produce intermediates. The released energy is absorbed by O₂ to produce superoxide anion radicals, and ROS are produced by a chain reaction. In the second type of mechanism, an electron crosses from the Sn system to T1, and the IC energy is transferred to the ground-state oxygen molecule (triplet oxygen molecule) such that it overcomes the spin-forbidden state and converts into singlet oxygen (¹O₂).^{44–46}

After ROS are produced by the material, they mainly clear or kill cells and bacteria through penetration. Their ability to kill cells can be attributed to three related mechanisms: direct cytotoxicity to cells, damage to the cellular vascular system, and induction of a strong inflammatory response in the body.⁴⁷ These three mechanisms eventually cause the body's immune response to be triggered, resulting in cell death.⁴⁴ To kill bacteria, ROS mainly rely on strong oxidation to destroy the bacterial cell membrane, increase the permeability of the bacterial cell membrane, and cause outflow of intracellular substances, eventually leading to bacterial inactivation.^{48–50} Moreover, ROS destroy bacterial nucleotide repair enzymes and genetic materials,⁴² affect bacterial biosynthesis, and subsequently inhibit and kill bacteria. (Figure 2)

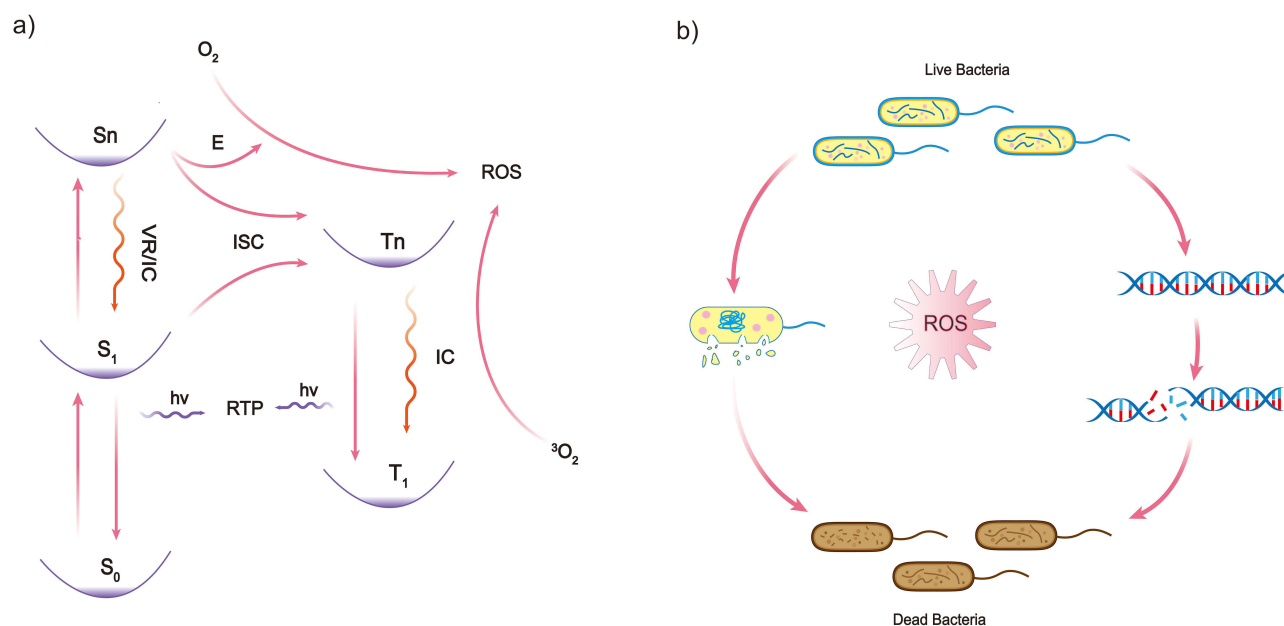


Figure 2 Mechanism of bioimaging and generation of ROS. (a). The Jablonski diagram, which is the mechanism of bioimaging. (b). Antibacterial mechanism of ROS.

Application of RTP Materials in Medicine

Application of RTP Materials in Bioimaging

Currently, conventional bioimaging techniques used in clinical practice include Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Positron Emission Tomography (scan) (PET).⁵¹ MRI is primarily used for soft tissues imaging, but it has poor sensitivity when it comes to examining the lungs and gastrointestinal tract, and the examination process is relatively time-consuming.⁵² CT offers higher resolution in soft tissue imaging, but there is a certain degree of ionizing radiation, which is harmful to the human body.⁵³ PET is more focused on functional imaging, but it offers relatively low resolution.⁵⁴ In the field of materials science, the research of bioimaging applications has also made great progress, such as quantum dots,⁵⁵ metal nanoparticles and so on.⁵⁶ Quantum dots also have large Stokes shift, which can be used for single molecule imaging, super-resolution imaging and three-dimensional imaging. However, compared with RTP materials, some quantum dots, especially those containing lead and chromium, are toxic to living cells and cause damage to organisms and the environment.⁵⁷ In addition, the long-life characteristics of RTP materials eliminate the interference of biological autofluorescence which occurs in traditional optical bioimaging, allowing in vivo imaging without real-time external excitation. Therefore, the application of RTP materials in bioimaging can enhance the sensitivity and specificity of in vivo imaging, and provides higher imaging SNR, which results in higher spatial and temporal resolution as well as imaging efficiency. To further meet the needs of in vivo biological imaging, the key to RTP materials research is developing substances with appropriate excitation wavelengths, long lifetimes, and effective red light emission. Gao et al summarized two methods to improve the phosphorescence properties of RTP materials:

(1) Heteroatoms, heavy atoms or carbonyl groups with lone pair electrons are introduced to increase the spin-orbit coupling (SOC) and promote the ISC process.⁵⁸

(2) The nonradiative relaxation pathway is suppressed by polymer-assisted methods, host-guest combination, etc., thereby stabilizing triplet excitons in a rigid environment.⁵⁸

In the past five years, through the unremitting efforts of researchers, remarkable progress has been made in this field. For example, Xu et al successfully developed a series of ultralong organic phosphorescent (UOP)-based photosensitizers (PSs) with long-lived triplet excited states for bacterial imaging and photodynamic therapy (PDT);⁵⁹ the pseudorotaxane polymer constructed by Zhou et al through host-guest interactions between cucurbit[n]urils (CBs) and hyaluronic acid (HA)-4-(4-bromophenyl)pyridin-1-ium bromide (BrBP) exhibited an ultralong RTP lifetime and an efficient phosphorescence quantum yield in aqueous solution.⁶⁰ In addition, many studies have shown that pure organic RTP materials can be used for bioimaging in living mice (Table 1). For example, Xiao et al first obtained organic room-temperature phosphorescent materials with long wavelengths and long lifetimes through a host-guest doping strategy, which showed good tissue penetration ability for bioimaging and enabled successful realization of tumor imaging in living mice.²⁷

However, in practical biomedical applications, RTP materials still face other problems that need to be solved. First, owing to the relatively short excitation wavelength of RTP materials, deep tissue penetration is still a key challenge. In other words, obtaining high-efficiency phosphorescence under visible light excitation, especially near-infrared (NIR) light excitation, is still a key challenge. Therefore, Zhao et al proposed a practical method for constructing organic RTP materials with near-infrared wavelengths and ultralong lifetimes and successfully prepared several organic RTP materials with near-infrared wavelength emission and significantly long lifetimes.¹¹ In addition, since the microenvironment inside a tumor is highly hypoxic in the organism, tumor cells grow in a disorderly manner. Therefore, achieving accurate RTP hypoxia imaging, which can help effectively locate hypoxic tumors, can make great contributions to the diagnosis and treatment of tumors. For example, Zhang et al synthesized a J-aggregation-induced second near-infrared phosphorescent material based on 5,15-bis(2,6-bis(dodecyloxy)phenyl)-porphyrin platinum(II) (PpyPt), which has good biological hypoxia-sensing potential.⁶¹ Therefore, RTP materials are expected to show superior potential in deep intraoral tumor imaging.

Application of RTP Materials in Tumor Therapy

Cancer has become an important disease which threatens people's life and health. Traditional treatment methods mainly include radiotherapy, chemotherapy, and surgical resection, which may cause great damage to body cells and may not be

Table I The Experimental Progress and Research of RTP Materials in the Field of Bioimaging

Year	Researchers	Material	Excitation Wavelength/ nm	Experimental Subject	Phosphorescence Quantum Yield /%	Phosphorescence Lifetime
2017	S.M.AliFatemi et al ²⁷	C-C4-Br nanocrystals	/	MAD-MB 231	11	0.14s
2018	Shi-Ying Li et al ²⁸	Cancer cell membrane@Pt(II) porphyrinic metal organic framework (mPPt)	405	4T1 cell COS7 cell RAW 264.7 cell	/	6.6ms (1%O ₂)
2018	Zhuang Lv et al ¹²	Hydrophilic phosphorescent starburst Pt(II) porphyrins	405	HeLa cell	6.22	868ms
2020	Letian Xu et al ²²	Ultralong organic phosphorescent-based PSs (SeDCz)	400–800	aureus Mouse	39.7	34ms
2020	Wei-Lei Zhou et al ²³	Spherical CB[8]/HA–BrBP pseudorotaxane polymer	/	A549 cell HeLa cell KYSE-150 cell	7.58	4.33ms
2021	Yunsheng Wang et al ²⁹	The host–guest doping systems based on M–CH3 and M–C2H5	365	HeLa cell HCC-LM3 cell	43	/
2021	Heqi Gao et al ²¹	Pure organic carbazolecontaining keto derivatives	365	4T1 cell BALB/c nude	51.59	801ms
2022	Fuming Xiao et al ²⁴	DMAPy/BPO guest–host materials	365	BALB/c nude 4T1 cell	3.1	70ms
2022	Wansu Zhang et al ²⁶	NIR-II 5.15-bis (2,6-bis (dodecyloxy) phenyl)-porphyrin platinum(II) (PpyPt) with J-aggregation	505 808	4T1 cell	/	35.33ms
2023	Kai Chang et al ³⁰	Phosphorescence nanoparticles (NPs) by phenothiazine derivatives and an amphiphilic triblock copolymer of PEG-b-PPG-b-PEG (F127) by a top-down method	365	CTCs	22.9	45ms
2024	Yeyun Zhao et al ²⁵	Fused-ring pyrrole-based structures long wavelength emissive	764	4T1 cell HeLa cell MCF-7 cell	1.13 0.65	210.2ms

able to cure the tumor and prevent recurrence. To overcome the disadvantages of traditional treatment methods, nano-targeted delivery system, photothermal therapy (aPTT) and photodynamic therapy (aPDT) of nanomaterials have become new research directions. nano-targeted delivery system mainly uses polymer-based nanocarriers and lipid-based nanocarriers to transport drugs to targeted sites and release drugs,^{62,63} which achieves drug aggregation at the tumor site and reduces systemic side effects caused by traditional chemotherapeutic drugs.⁶⁴ However, this treatment method has problems such as premature and uncontrollable drug release,⁶⁵ resulting in a greatly reduced effect of cancer treatment. The aPTT therapy operates by converting light energy into heat energy through materials, and releasing heat energy in local tissues to achieve tumor cell damage.⁶⁶ The aPDT therapy operates by releasing ROS through materials, which gets rid of the limitation of drug therapy. At the same time, the controllable ROS release of materials can achieve precise treatment of cancer.^{67,68}

At present, the nanomaterials used for aPTT and aPDT therapy mainly include gold nanoparticles, graphene oxide, carbon dots, etc.^{69–72} Gold nanoparticles are commonly used in aPTT therapy, which have a low incidence of complications, and there are various methods for the synthesis of gold nanoparticles.^{73,74} However, the materials have high cytotoxicity and are easy to deposit in human body,⁷⁵ making it difficult to achieve wide clinical application. Graphene oxide and carbon dots are commonly used in aPDT therapy, which have the characteristics of high ROS production rate and low toxicity. However, the limited synthesis method of materials leads to a single structure and poor stability, and there may be individual differences in clinical treatment effects.^{76–78} In recent years, RTP materials have been continuously developed. In addition to achieving high ROS production and precise targeting capabilities and combining the basic characteristics of low toxicity and high stability, RTP materials also have characteristics of diverse structures and flexible synthesis methods. It may be possible to synthesize the corresponding molecules according to the physical and chemical environment of patient's body, which may greatly improve the anti-cancer effect of the materials and have great development potential in tumor treatment.

In the early stage of the development of RTP materials, people mainly focused on inorganic metal RTP materials. Alemayehu et al used corroles (H3[p/mTCPC]), gold and their complexes to prepare Au[p/mTCPC]. After coincubation of the material with a rat model of bladder cancer for 24 h, the tumor tissue was examined under 435 nm light excitation irradiation. The mortality rate of the tumor cells was as high as 50%, but the surrounding healthy tissues were affected to some extent.⁷⁹ Zhao et al obtained the nanoprobe Gd[PC]@ZIF-8 by using a host–guest system. Through detection of the PDT performance, the researchers found that its $^{1}O_2$ quantum yield was as high as 0.88. After coincubation with HeLa cells, the survival rate of HeLa cells was reduced to 30%, which provided a new idea for PDT for tumor treatment.⁸⁰

Since inorganic metal RTP materials may have certain toxicity, the development of organic RTP materials has further advanced PDT in the field of tumor therapy.(Table 2) Miao et al prepared N-doped carbon dot (CND)-CY3.5 nanocomposites via a hydrothermal method using triethylenetetraminehexaacetic acid (TTHA) as the raw material and successfully achieved a high $^{1}O_2$ quantum yield of 0.63 in a water environment. In *in vitro* tumor experiments, CNDs killed 99.9% of HeLa cells; at the same time, after the material was coincubated with the tumor model mice, obvious necrosis was detected in the tumor tissue of the mice, whereas the surrounding tissue was not damaged, indicating that this material was good and had a specific tumor clearance ability.⁴⁶ However, traditional excitation is commonly excited by UV, which may lead to gene mutation and cell damage after patients exposure. So the proposal of near-infrared two-photon excitation(TPE) avoids cells damage caused by excitation light, improves the tissue penetration depth of excitation light, and achieves the removal of deep tumors.⁸¹ Xu et al designed BF2DCz-bovine serum albumin (BSA) nanoparticles (NPs) based on TPE-PDT with an organic RTP material. After TPE, the diffusion depth of the NPs reached 100 nm, and the quantum efficiency of $^{1}O_2$ reached 90.3%, leading to successful and accurate killing of tumor cells in deep tissue.⁸¹ In tumor therapy, organic RTP materials have the advantages of high efficiency, low damage and low toxicity, which are not achievable with inorganic RTP materials. Moreover, because of the more diverse design of organic RTP materials, they can be improved according to different physical and chemical environments of cancer patients themselves, so that the materials are more in line with patients' needs and further improve the accuracy of tumor diagnosis and clearance rate of tumors. Therefore, with the continuous development of RTP materials, their application in tumor treatment has gradually become possible in both the oral field and the clinical field.

Table 2 The Experimental Progress and Research of RTP Materials in Tumor Therapy

Material Category	Researchers	Material	Excitation Wavelength	ROS Quantum Yield	Tumor Cell	Maximum Cell Kill Rate
Metal RTP	Alemayehu et al ³¹	Au[p/mTCPC]	435nm	/	Rat Bladder Cancer Cell Line AY2	50%
	Zhao et al ³²	Gd [PC] @ ZIF – 8	365nm	0.88	HELA cell	40.96%
	Lv et al ³⁴	Ir-P (ph) 3	475nm	0.17	HELA cell	97.7%
	Huang et al ³⁵	[Ru(bpy-tma)3](ClO4)8. [Ru(bpy-teta)3](ClO4)8. [Ru(bpy-tbua)3](ClO4)8.	450 nm and 800 nm	450 nm: In methanol:0.92–0.99 In D2O:0.49–0.67 800 nm: Not specified	HELA cell	phototoxicity index (for three materials): 450 nm:50\32.5\23.6 800 nm:250\92.6\69.4
Organic RTP	Miao et al ¹⁵	CNDs-Cy3.5 nanocomposites (Triethylenetetramine hexaacetic acid (TTHA))	365nm	0.63	HELA cell, Mice with HELA cells	HELA cell:99.9% Mice with HELA cells: tumors were significantly inhabited
	Xu et al ³³	1,3-di (9Hcarbazol-9-yl)propane-1,2-dione (BF2DCz)	800 nm+405 nm multiphoton excitation	90.3%	HeLa cells and MCF-7 cells (breast cancer cell line)	Almost all cancer cell dead A specified depth of cells in tumour spheroids dead
	Shi et al ³⁶	4,7-dibromo-5,6-dicarbazolyl-2,1,3-benzothiadiazole (DBCz-BT)	475nm	/	HELA cell, Mice with HELA cells	HELA cell:80%, Mice with HELA cells: five times smaller and keeping stable.

Application of RTP Materials for Antibacterial Treatment

Antibiotics are the main means for people to inhibit bacteria and prevent infection.⁸² However, with the use of antibiotics, the emergence of antibiotic-resistant bacteria has become a major obstacle to their further use.^{83–85} Therefore, the development of new antibacterial methods is highly important for anti-infection and disease treatment. In recent years, related antibacterial materials such as LL37 peptide⁸⁶ and titanium dioxide nanoparticles⁸⁷ have achieved the clearance of drug-resistant bacteria and broadened the spectrum of antibacterial materials. At the same time, with the development of nanomaterials, it provides various new ideas in antibacterial infection and prevention of infection complications, which is of great significance.

According to related research, nano-targeted delivery system and aPDT therapy are two feasible methods in the field of nanomaterial-based antibacterial research.^{88–90} Due to the dispersion of bacteria, more nanocarriers may be needed to achieve bacteria clearance. Meanwhile, the antibacterial function of nanocarriers is mainly achieved by drugs, which may lead to failure due to bacterial resistance.^{91,92} But aPDT therapy of nanomaterials ensures the antibacterial effect through generation of ROS rather than traditional drugs, which can not only clear bacteria but also avoid the side effects of traditional drugs.⁹³ At the same time, aPDT therapy can clear more bacteria with little amount of material via the excellent diffusion ability of ROS. At present, most of the nanomaterials used in aPDT therapy are porphyrin-based nanomaterials. This material employs porphyrin as a photosensitizer (PS), utilizing precious metals, metal oxides, and carbon materials as carriers for the porphyrin. And through encapsulation and photoexcitation, it achieves the release of ROS.⁷³ In contrast with porphyrin-based nanomaterials, in addition to its basic characteristics such as low toxicity, RTP materials have unique targeted antibacterial capabilities.^{31,42} Due to the high flexibility of RTP materials, it may be possible to specifically target the corresponding bacteria by improving the molecular structure and combining with antibacterial peptides⁹⁴ to achieve accurate clear of the target bacteria, reducing the likelihood of a diminished antibacterial effect and minimizing damage to healthy flora, which may be caused by the widespread diffusion of ROS.

In the past ten years, RTP material antibacterial therapy has achieved promising results in the oral field. (Table 3) Klepac-Ceraj et al prepared methylene blue (MB)-loaded polylactic acid-glycolic acid (PLGA) copolymers, namely MB-PLGA NPs, which were cocultured with oral flora culture medium and irradiated with 665 nm red light. The results revealed that the biofilm inhibition rate reached 50%, which provides a basis for the treatment of periodontitis and other diseases with RTP materials.⁹⁵ Golmohamadpour et al synthesized three different metal organic framework (MOF)-ICG nanomaterials. Through coculture of *Enterococcus faecalis* and PDT experiments, the antibacterial ability of AI-101-ICG was found to reach 89%, which provides a strong basis for the use of RTP materials for the treatment of oral periapical periodontitis.⁹⁶

However, there are three main shortcomings of RTP materials antibacterial therapy, which are easy aggregation, poor water solubility and unstable chemical properties. At present, most RTP materials need to be carried by water phase, so poor water solubility may lead to a decrease in their availability. At the same time, due to the shortcomings of easy aggregation and instability of materials, RTP particles in the solution may aggregate into large particles and precipitate, and even directly decompose due to changes in physical and chemical environment such as temperature, which ultimately leads to a large amount of material loss and a great decrease in antibacterial effect. So researchers have proposed several improvement strategies for overcoming the limitations of RTP materials as PSs,^{32,47} which lay a foundation for the application of RTP materials in the field of antibacterial.

(1) RTP materials are combined with nanomaterials to improve their water solubility, hinder their aggregation, and promote the production of ROS to improve their antibacterial ability.⁹⁷

(2) The triplet exciton decay of RTP materials is regulated to prolong the generation of ROS and improve their antibacterial ability.⁹⁸

(3) The degree of aggregation of an RTP material is adjusted to hinder the quenching caused by aggregation, prolong the generation and action time of ROS, and improve its antibacterial ability.^{83,99}

(4) The positive and negative electrostatic interactions of materials are utilized to increase their ability to bind with bacteria, thereby improving their antibacterial ability.^{100,101} (Figure 3)

Table 3 The Experimental Progress and Research of RTP Materials for Antibacterial Treatments

Material Category	Researchers	Material	Excitation Light	Bacteria	Biofilm/Bacterial Growth Inhibition Rate				
Inorganic Metal RTP	Golmohamadpour et al ⁴⁹	MOF-ICG (MOF: High capacious metal organic framework–Fe-101, Al-101 and Fe-88; ICG: indocyanine green).	810nm	E. faecalis	Biofilm: Fe-88: 37.54% Fe-101: 47.01% Al-101: 53.68% Bacteria: Fe-88: 60.72% Fe-101: 45.12% Al-101: 62.67%				
	Wang et al ⁵³	Ag-NPs@Ti	420–480nm; 480–550nm	E. coli; S. aureus	Bacteria: during culturing for 24 h				
					E. coli		99%		
					S. aureus		90%		
	Jolanta Pulit-Prociak et al ⁵⁴	A series of PVA-based compositions with zinc oxide, silver and copper nanoparticles	/	Coli; Aeruginosa; S. aureus	Bacteria: the data in the table represent MIC(ppm)				
					Bacteria Material		E.Coli	P.Aeruginosa	S.aureus
					NanoZn	K1	117	15,000	15,000
						K2	781	25,000	12,500
						K3	3125	25,000	12,500
					NanoAg	K4	31	125	250
						K5	125	125	125
						K6	13	50	50
						K7	50	50	50
					NanoCu	K8	125	31	250
						K9	50	50	25
						K19	50	50	25

(Continued)

Table 3 (Continued).

Material Category	Researchers	Material	Excitation Light	Bacteria	Biofilm/Bacterial Growth Inhibition Rate																																																																																																			
Organic RTP	Klepac-Ceraj et al ⁴⁷	MB-PLGA NPs (MB: methylene blue; PLGA: lactic-co-glycolic).	665nm	Polymicrobial oral biofilms	Biofilm:50%																																																																																																			
	Elham Gholibegloo et al ⁵⁵	GO-Car@ICG; GO-Car/HAp@ICG (Car: a simple naturally occurring dipeptide; HAp: Hydroxyapatite).	810nm	S. mutans	Biofilm: GO-Car@ICG: 95.5% GO-Car/HAp@ICG: 93.2% Bacteria: GO-Car@ICG: 63.8% GO-Car/HAp@ICG: 56.8%																																																																																																			
	Akbari et al ⁴⁸	NGO-ICG (NGO: nano-graphene oxide; ICG: indocyanine green).	810nm	E. faecalis	Biofilm:99.4% Bacteria:90.6%																																																																																																			
	Sun et al ⁴⁶	CDs/ PVA composite films (raw materials: diethylenetriaminepentaacetic acid; PVA: polyvinyl alcohol).	Vis and UV (no detailed wavelength)	E. coli; S. aureus; B. cinerea	Bacteria: different concentration of RTP P-CDs <table><tr><th> Light Bacteria </th><th>Vis</th><th>UV</th><th>Vis</th><th>UV</th><th>Vis</th><th>UV</th><th>Vis</th><th>UV</th></tr><tr><td rowspan="3">E. coli</td><td colspan="8">Concentration (µg/mL)</td></tr><tr><td colspan="2">5</td><td colspan="2">10</td><td colspan="2">50</td><td colspan="2">100</td></tr><tr><td>18.50%</td><td>29.60%</td><td>44.59%</td><td>77.52%</td><td>77.61%</td><td>87.46</td><td>95.80%</td><td>99.25%</td></tr><tr><td rowspan="3">S. aureus</td><td colspan="8">Concentration (µg/mL)</td></tr><tr><td colspan="2">5</td><td colspan="2">10</td><td colspan="2">20</td><td colspan="2">30</td></tr><tr><td>46.46%</td><td>61.77%</td><td>76.71%</td><td>78.93%</td><td>93.27%</td><td>97.47%</td><td>99.09%</td><td>99.91%</td></tr><tr><td rowspan="4">B. cinerea</td><td colspan="8">Concentration (mg/mL)</td></tr><tr><td colspan="8">2</td></tr><tr><td colspan="4">Vis</td><td colspan="4">UV</td></tr><tr><td colspan="4">36.56%</td><td colspan="4">36.17%</td></tr></table>									Light Bacteria	Vis	UV	Vis	UV	Vis	UV	Vis	UV	E. coli	Concentration (µg/mL)								5		10		50		100		18.50%	29.60%	44.59%	77.52%	77.61%	87.46	95.80%	99.25%	S. aureus	Concentration (µg/mL)								5		10		20		30		46.46%	61.77%	76.71%	78.93%	93.27%	97.47%	99.09%	99.91%	B. cinerea	Concentration (mg/mL)								2								Vis				UV				36.56%				36.17%		
Light Bacteria	Vis	UV	Vis	UV	Vis	UV	Vis	UV																																																																																																
E. coli	Concentration (µg/mL)																																																																																																							
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	18.50%	29.60%	44.59%	77.52%	77.61%	87.46	95.80%	99.25%																																																																																																
S. aureus	Concentration (µg/mL)																																																																																																							
	5		10		20		30																																																																																																	
	46.46%	61.77%	76.71%	78.93%	93.27%	97.47%	99.09%	99.91%																																																																																																
B. cinerea	Concentration (mg/mL)																																																																																																							
	2																																																																																																							
	Vis				UV																																																																																																			
	36.56%				36.17%																																																																																																			

	Chao et al ⁴³	BP/BQD NPS (BQD: 2-butyl-1H-benzo[de] isoquinoline 1,3 (2H)-dione; BP: benzophenone).	White light and UV light (480nm)	E. coli; S. aureus	Light		
					Bacteria	White light	UV light
					E. coli	26%~28%	98%~99%
	Wang et al ⁵⁶	PNPs (made by DBCzBT: 4,7-dibromo-5, 6-di (9H-carbazol-9-yl) benzo[c] ^{1,2,5} thiadiazole).	410nm	E. coli; MASA	S. aureus	94%~96%	100%
					Bacteria: the concentration of materia is 0.8mg/mL. CFU: E. coli and MASA have little difference		
					Time	0min	10min
					Bacteria		
					E. coli	0%	100%
					MASA	0%	100%

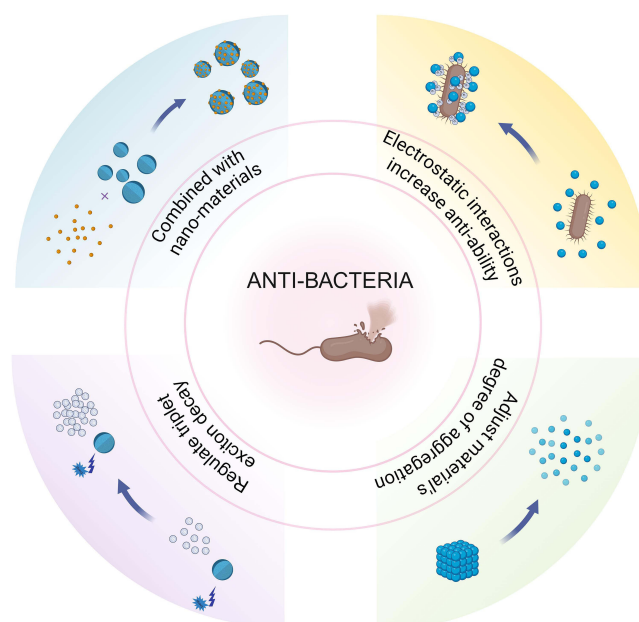


Figure 3 Four improvement strategies for overcoming three limitations of RTP materials as PSs.

Notes: Created in BioRender. Zhang, Y. (2024) <https://BioRender.com/e59q768>.

According to the strategies, Akbari et al prepared nano-graphene oxide (NGO)-indocyanine green (ICG), improved the photodynamic characteristics of ICG, and cocultured the material with faecal cocci. After light irradiation, the number of bacteria detected decreased by 90.6%, and the biofilm formation rate decreased to 0.06%.¹⁰²

Owing to the gradual improvement in people's living standards, the incidence of oral diseases such as dental caries and periapical periodontitis has gradually increased. Moreover, in the process of treating oral diseases, bacteria such as *Enterococcus faecalis* and *Porphyromonas gingivalis* have important impacts on the development of diseases.^{103–105} Therefore, the ability of RTP materials to inhibit such bacteria provides a new direction for clinical treatment, and the realization of efficient inhibition of various oral bacteria is highly important for the control and treatment of oral periodontitis and other diseases.

Summary and Outlook

In recent years, RTP materials have made significant progress in biomedical fields such as in vivo bioimaging, tumor therapy, and antibacterial. Based on these results, we believe that RTP materials also have great application potential in the oral field. First of all, RTP material has excellent optical properties, which can provide high SNR and good tissue penetration. At the same time, with the unique targeting ability of the material to tumor cells, RTP materials can be used for accurate positioning and diagnosis of oral tumors and judgment of the development stage of periodontitis inflammation. At the same time, RTP material has good tumor killing ability, and due to its various synthesis methods, its molecule can be designed according to individual differences of patients, making the material more suitable for the individual microenvironment of patients, and further improving the detection rate and tumor killing rate of oral cancer. Secondly, in terms of antibacterial properties, RTP materials have good antibacterial properties and can effectively inhibit oral bacterial infection. We hope that it can be used for the sterilization of dental related instruments, which can reduce the problems of long time and high energy consumption of traditional instruments sterilization. It can also accurately target specific bacteria and clear them through different molecular structures, such as the removal of oral pathogenic bacteria in patients with periodontitis and pulpitis, so as to improve the therapeutic effect and quality of life of patients.

However, RTP materials may also have some problems in the treatment of these diseases. For example, in oral tumor bioimaging, the resolution of RTP may be affected by material concentration, so when the resolution is reduced due to the decrease of material concentration, the accuracy of detection and diagnosis of subtle lesions may decrease. In addition, in the complex oral environment, it is necessary to determine whether RTP materials can effectively kill deep

tumor cells and reduce tumor recurrence rate. Besides, the antibacterial effect of RTP materials may have the problem of poor durability. So more materials will be needed in sterilization of instruments and treatment of periodontitis and dental caries, resulting in high prices and waste of medical resources. Therefore, there are two urgent problems to be solved in the clinical application of RTP materials. On the one hand, RTP materials show concentration dependence when used for tumor imaging, tumor therapy and antibacterial purposes, and the effect windows of different materials are significantly different. So in clinical applications, the utilization of RTP materials requires precise control of the concentration and effect duration. On the other hand, the three major applications of RTP materials in medicine are often excited by ultraviolet or infrared light, so even a short time of irradiation may have adverse effects on the human body.

Based on the above problems, we expect that it is necessary to develop RTP materials that can be excited by visible light and can be used sustainably to improve the safety and comfort of treatment. From a clinical point of view, this not only avoids the side effects of excitation light like ultraviolet and infrared light, but also reduces waste of material resources due to the poor treatment effect caused by decomposability of the materials. From an economic point of view, for oral diseases that require repeated use of materials for antibacterial purposes, such as periodontitis, dental caries, etc., reducing the cost of RTP materials is also crucial for future development, which can be achieved by sustainable and visible-light-excited RTP materials. This can not only reduce the economic burden of patients, but also increase the accessibility and application range of materials. So RTP materials can give full play to their potential, provide innovative solutions for oral cancer and antimicrobial therapy, and ultimately contribute to improving human health and well-being.

Abbreviations

RTP, room-temperature phosphorescent; SNR, signal-to-noise ratio; ROS, reactive oxygen species; S₀, ground state; S_n, singlet excited state; VR, vibrational relaxation; IC, internal conversion; ISC, intersystem crossing; T_n, triplet excited state; singlet oxygen, ¹O₂; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography; SOC, spin-orbit coupling; UOP, ultralong organic phosphorescent; PSs, photosensitizers; PDT, photodynamic therapy; NIR, near-infrared; NPs, nanoparticles.

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Disclosure

The authors declare that they have no competing interest in this work.

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