

Functional Materials for Subcellular Targeting Strategies in Cancer Therapy: Progress and Prospects

Yanxiang Cheng, Zhen Qu, Qian Jiang, Tingting Xu, Hongyun Zheng, Peng Ye, Mingdi He, Yongqing Tong,* Yan Ma,* and Anyu Bao*

Neoadjuvant and adjuvant therapies have made significant progress in cancer treatment. However, tumor adjuvant therapy still faces challenges due to the intrinsic heterogeneity of cancer, genomic instability, and the formation of an immunosuppressive tumor microenvironment. Functional materials possess unique biological properties such as long circulation times, tumor-specific targeting, and immunomodulation. The combination of functional materials with natural substances and nanotechnology has led to the development of smart biomaterials with multiple functions, high biocompatibilities, and negligible immunogenicities, which can be used for precise cancer treatment. Recently, subcellular structure-targeting functional materials have received particular attention in various biomedical applications including the diagnosis, sensing, and imaging of tumors and drug delivery. Subcellular organelle-targeting materials can precisely accumulate therapeutic agents in organelles, considerably reduce the threshold dosages of therapeutic agents, and minimize drug-related side effects. This review provides a systematic and comprehensive overview of the research progress in subcellular organelle-targeted cancer therapy based on functional nanomaterials. Moreover, it explains the challenges and prospects of subcellular organelle-targeting functional materials in precision oncology. The review will serve as an excellent cutting-edge guide for researchers in the field of subcellular organelle-targeted cancer therapy.

imaging and chemical labeling techniques have facilitated the exploration of the biological processes occurring within organelles, namely, mitochondria, endoplasmic reticulum (ER), Golgi apparatus, lysosome, and nucleus, in both physiological and pathological states.^[1–3] Note that during carcinogenesis and tumor progression and treatment, different oncogenic, transcriptional, and metabolic abnormalities synergistically create hostile microenvironments, leading to persistent alterations in cell organelles or subcellular structures including mitochondria,^[4,5] ER,^[6,7] Golgi apparatus,^[8] lysosome,^[9,10] nucleus,^[11] and cell membrane (CM)^[12] (Figure 1). For example, the mitochondrial network can be divided into different subgroups that govern the bioenergetic capacities of non-small lung cancer (NSCLC) cells. Targeting these subcellular structures in tumor cells enables specific recognition of tumor cells and provides insights into tumor proliferation, metabolism, and metastasis status.^[13] Alterations of mitochondrial morphology are observed in progressive serous ovarian cancer and potentially promote tumor cell viability under non-permissive conditions.^[14] Thus, monitoring the changes in the functions or morphologies of organelles using appropriately designed materials offers potential diagnostic tools for various cancers.^[15–16] For instance, Fang et al. developed a near-infrared (NIR) fluorescent

1. Introduction

Cell organelles are unique structures that maintain the normal functioning and operation of cells. Advances in subcellular

morphologies of organelles using appropriately designed materials offers potential diagnostic tools for various cancers.^[15–16] For instance, Fang et al. developed a near-infrared (NIR) fluorescent

Y. Cheng
Department of Gynecology
Renmin Hospital
Wuhan University
No.238 Jiefang Road, Wuchang, Wuhan 430060, P. R. China

Z. Qu, Q. Jiang, M. He, Y. Ma
Department of Blood Transfusion Research
Wuhan Blood Center (WHBC)
HUST-WHBC United Hematology Optical Imaging Center
No.8 Baofeng 1st Road, Wuhan, Hubei 430030, P. R. China
E-mail: ma.y@whblood.org.cn

T. Xu
Department of Clinical Laboratory
Wuhan Blood Center (WHBC)
No.8 Baofeng 1st Road, Wuhan, Hubei 430030, P. R. China

H. Zheng, Y. Tong, A. Bao
Department of Clinical Laboratory
Renmin Hospital
Wuhan University
No.238 Jiefang Road, Wuchang, Wuhan 430060, P. R. China
E-mail: tytsing@whu.edu.cn; bay@whu.edu.cn

P. Ye
Department of Pharmacy
Renmin Hospital
Wuhan University
No.238 Jiefang Road, Wuchang, Wuhan 430060, P. R. China

 The ORCID identification number(s) for the author(s) of this article can be found under <https://doi.org/10.1002/adma.202305095>

DOI: 10.1002/adma.202305095

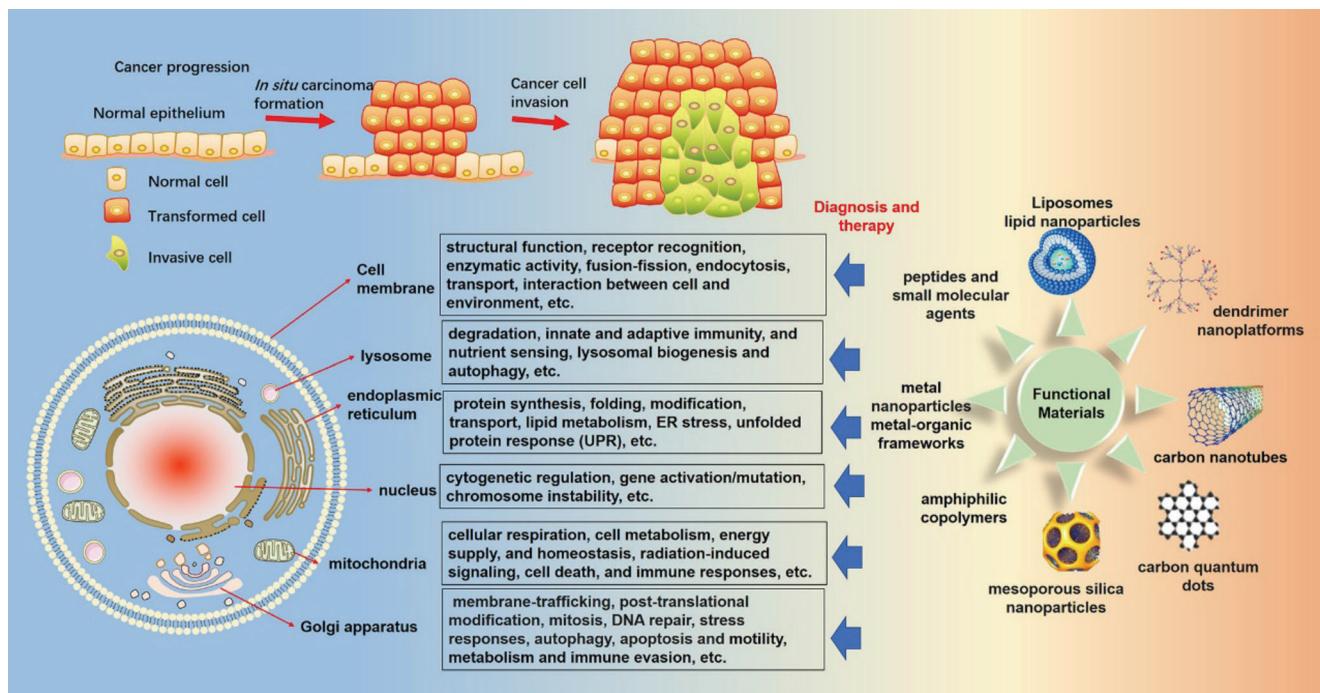


Figure 1. Targeting subcellular structures is a promising strategy in precision oncology. Subcellular structures, such as mitochondria, endoplasmic reticulum, Golgi apparatus, lysosome, nucleus, and cell membrane, are altered during cancer initiation and progression. Functional materials are applied for the diagnosis and therapy of cancers by targeting subcellular structures.

probe for the sensitive detection of mitochondrial pH and mitophagy. This probe demonstrates an adequate ability for fluorescence imaging of tumor-bearing mice.^[17] Yang et al. designed a tetraphenylethylene (TPE)-based fluorescent probe (TPE-PH-KD) based on a quinolinium group. This probe was located in the mitochondria and lysosomes of cancer cells and rapidly responded to viscosity and pH changes. Thus, it can be an efficient tool for highly selective visualization of tumors at the organ level.^[18]

Pharmacological or molecular targeting techniques that directly modulate organelle function exhibit significant potential for application in disease improvement and treatment.^[19–22] With the ongoing exploration of antitumor drugs and advancements in pharmacological research, numerous chemotherapeutic drugs and bioactive substances with abilities to target subcellular structures or organelles have been identified. A list of some Food and Drug Administration (FDA)-approved cell organelle-targeting drugs is provided in Table 1. Trifluoperazine, mitoxantrone, and pyrvonium pamoate, which are FDA-approved drugs used for targeting mitochondria,^[36] demonstrate potent antitumor effects by inducing mitochondria-mediated apoptosis.^[24–25,37] Utilizing the organelle-targeting properties of these drugs, researchers have developed novel combination drug regimens that further enhance the efficacies of antitumor treatments.^[38–41] For example, the combination of carboplatin and photodynamic therapy (PDT) utilizing 9-hydroxyphorphorhodaïne enhances the cytotoxicities and apoptosis of laryngeal cancer cells via the mitochondrial and ER apoptosis pathways.^[42] Zhang et al. designed a multifunctional nanodrug, IR780@Pt nanoparticles (NPs), by combining a cisplatin (CDDP) prodrug (Pt-CD) with a mitochondria-

targeting NIR photosensitizer (PS), IR780. This nanodrug induces mitochondrial dysfunction in cancer cells, reduces deoxyribonucleic acid (DNA) repair activity, and substantially weakens mitochondrial–nuclear interactions.^[43] A combined strategy that targets subcellular structures or organelles offers distinct advantages. First, it reduces the therapeutic dosages required for individual drug treatments, thereby minimizing drug-related side effects. Second, the combination of two or more drugs can exert synergistic antitumor effects and mitigate drug resistance. Third, the application of diverse targeting strategies enhances the precision of drug delivery.^[44–46] Nevertheless, these drugs need to be specifically transported to the target organs, tissues, cells, and even specific organelles using efficient drug delivery systems, for instance, nano-drug delivery systems.^[47]

Accordingly, this review examines the current advancements in tumor diagnosis based on subcellular structures or organelles both in vitro and in vivo. Additionally, it investigates the delivery methods and molecular strategies of functional materials that specifically target subcellular structures or organelles in tumor cells, including mitochondria, nucleus, endoplasmic reticulum, lysosome, Golgi apparatus, cell membrane, and multi-organelle targeting strategies. And this review covers a wide range of functional materials, such as liposomes, metal nanoparticles, metal-organic frameworks, dendrimer nanoplatforms, carbon nanotubes, mitochondria-targeting mesoporous silica nanoparticles, carbon quantum dots, amphiphilic copolymers, and small molecular compounds. Furthermore, this review discusses the future prospects of functional materials with organelle-level specificities in achieving precise tumor diagnosis and treatment. Developments in this field are of significant importance in

Table 1. FDA-approved cell organelle-targeted drugs.

Drug	Molecular formula	Cancer/cells	Target/mechanism	Reference
Etoposide	C ₂₉ H ₃₂ O ₁₃	pancreatic cancer	mitochondria/apoptosis	[23]
Trifluoperazine	C ₂₁ H ₂₄ F ₃ N ₃ S	breast cancer	mitochondria/apoptosis	[24]
mitoxantrone	C ₂₂ H ₂₈ N ₄ O ₆	non-small cell lung cancer cell	mitochondria/apoptosis	[25]
pyrvium pamoate	C ₂₆ H ₂₈ N _{3.1/2} C ₂₃ H ₁₄ O ₆	Pancreatic Cancer	mitochondria/apoptosis	[26]
olaparib	C ₂₄ H ₂₃ FN ₄ O ₃	oesophageal carcinoma	PARP/DNA damage	[27]
doxycycline	C ₂₂ H ₂₄ N ₂ O ₈	cancer stem-like cells	DNA-PK/DNA damage	[28]
Sunitinib	C ₂₂ H ₂₇ FN ₄ O ₂	pancreatic cancer	Ire1α/ER stress	[29]
Carfilzomib	C ₄₀ H ₅₇ N ₅ O ₇	non-small cell lung cancer	GRP78/ER stress	[30]
Bortezomib	C ₁₉ H ₂₅ BN ₄ O ₄	breast cancer	GRP78/ER stress	[31]
celecoxib	C ₁₇ H ₁₄ F ₃ N ₃ O ₂ S	breast cancer	Golgi apparatus/anti-metastatic	[32]
hydroxychloroquine	C ₁₈ H ₂₆ ClN ₃ O	ovarian cancer	lysosome/Lysosomal Homeostasis	[33]
eliglustat	C ₂₃ H ₃₆ N ₂ O ₄	Melanoma	lysosome/lysosomal autophagy inhibition	[34]
Verteporfin	C ₈₂ H ₈₄ N ₈ O ₁₆	hepatocellular carcinoma	lysosome/lysosomal sequestration	[35]
Sulfisoxazole	C ₁₁ H ₁₃ N ₃ O ₃ S	breast cancer	endothelin receptor A/small extracellular vesicles	[35]

promoting innovation in tumor diagnostic and therapeutic approaches, eventually contributing to the realization of effective cancer treatments.

2. Mitochondria-Targeting Strategies for Tumor Diagnosis and Treatment

2.1. Mitochondria-Related Targets for Tumor Diagnosis

Mitochondrion is a cell organelle that generates energy for cells via cellular respiration. Mitochondria are also involved in many other cellular processes, including cellular homeostasis, metabolism, cell death, immune responses, etc.^[48] Structures, DNAs, and functions of mitochondria undergo changes in several types of cancers, and these alterations can be used as diagnostic markers.^[49] Due to mutations in oncogenes, tumor suppressor genes, and metabolic enzymes, many mitochondrial metabolic pathways are dysregulated during cancer development. These pathways comprise oxidative phosphorylation (OXPHOS), electron transport chain (ETC), tricarboxylic acid (TCA) cycle, one-C metabolism, fatty acid β-oxidation, and mitochondrial reactive oxygen species (ROS) generation. Altered mitochondrial metabolism leads to reprogramming of cellular metabolism to maintain rapid cell proliferation; consequently, cancer cells may utilize ROS to sustain tumor-promoting signaling pathways while avoiding death.^[50] For example, mutations in mitochondrial DNA (mtDNA) have been noticed in several types of cancers, and changes in mtDNA copy number and possible transfer of mtDNA sequences to the nucleus can also lead to certain cancers. In contrast, mutations in nuclear DNA-encoded mitochondrial genes can also affect mitochondrial metabolic function.^[51]

Previous studies have detected multiple proteins that regulate mitochondrial functions, including mitochondrial division, for instance, dynamin-related protein 1, and mitochondrial fusion, for example, mitofusins and optic atrophy 1. Targeted interferences with the expressions of these proteins significantly modulate mitochondrial functions.^[52] Therefore, iden-

tifying the key targets of cancer in mitochondria affords an attractive strategy for tailored and personalized cancer therapy. In primary acute myeloid leukemia (AML) cells Down-regulations of B-cell lymphoma 2 (Bcl2) interacting protein 3 like (BNIP3L)/Nix and sequestosome 1 (SQSTM1)/p62, two autophagy genes involved in mitochondrial clearance, have been observed. Leukemia cells lacking these autophagy genes are more sensitive to mitochondria-targeting drugs. These findings suggest that BNIP3L or SQSTM1 can potentially serve as prognostic markers for identifying AML patients who are suitable candidates for mitochondria-targeted therapies.^[53] Sirtuin 3 (Sirt3) belongs to a crucial member of the mammalian sirtuin protein family, which participates in the regulation of diverse cellular processes. As a major mitochondrial nicotinamide adenine dinucleotide-dependent deacetylase, Sirt3 plays a crucial role in controlling oxidative stress, metabolic homeostasis, and reprogramming of tumor cell energy pathways. Sirt3 takes part in the regulation of outer mitochondrial membrane permeability, a critical step in the initiation/progression of cell apoptosis.^[54] The other mitochondria-related targets, such as BTB and CNC homology 1 (BACH1),^[55] L-Carnitine and acylcarnitines,^[56] the heat shock protein 90 (HSP90)-pyruvate kinase muscle isozyme M2 (PKM2)-Bcl2 axis,^[57] sirtuins and OGG1-2a,^[58] and mitochondria-mediated apoptotic genes (BAK, PUMA, BID, BAX, and NOXA),^[59] can directly indicate the mitochondrial functions of tumor cells and can be used to estimate the efficacies of antitumor drugs.

2.2. Mitochondria-Targeting Drugs

Mitochondria-dependent oxidative metabolism is crucial for energy production and growth of certain cancer cells, rendering mitochondria-targeting drugs promising candidates for antitumor therapy.^[60] Quantities and morphologies of mitochondria are determined by mitochondrial dynamics, biogenesis, and mitophagy. Mitochondria-targeting antitumor drugs induce mitochondrial swelling, mitochondrial membrane potential ($\Delta\Psi_m$)

Table 2. Mitochondria-targeting drugs in cancer treatment.

Drug	Molecular formula	Classification	Target/mechanism	Reference
Melatonin	C ₁₃ H ₁₆ N ₂ O ₂	Approved metabolic drug	Mitochondrial dysfunction, activated AMPK/SIRT1 pathway, and pyroptotic death	[441–443]
5-Fluorouracil	C ₄ H ₃ FN ₂ O ₂	Chemotherapeutic drug	Depolarization of the mitochondrial membrane and disruption of calcium homeostasis	[444]
Gemcitabine	C ₉ H ₁₁ F ₂ N ₃ O ₄	Chemotherapeutic drug	Mitochondrial ultrastructure and function	[65]
Paclitaxel	C ₄₇ H ₅₁ NO ₁₄	Chemotherapeutic drug	Mitochondrial dysfunction and apoptosis	[445]
Cisplatin	C ₁₂ H ₆ N ₂ Pt	Chemotherapeutic drug	Mitochondrial dysfunction and apoptosis	[446]
Doxorubicin	C ₂₇ H ₂₉ NO ₁₁	Chemotherapeutic drug	Mitochondrial dysfunction and apoptosis	[447]
Pardaxin	C ₁₅₄ H ₂₄₈ N ₃₆ O ₄₅	ER-targeting peptide	Excessive mitophagy and mitochondria-mediated apoptosis	[448]
Ropivacaine	C ₁₇ H ₂₆ N ₂ O	Local anesthetic agent	Mitochondrial dysfunction and apoptosis	[449]
Mitoquinol mesylate (MitoQ)	C ₃₈ H ₄₉ O ₇ PS	Mitochondria-targeting antioxidant		[450–452]
Fraxetin	C ₁₀ H ₈ O ₅	Natural product	Mitochondrial dysfunction	[453]
Matairesinol	C ₂₀ H ₂₂ O ₆	Natural product	Mitochondrial impairment	[444]
Allicin	C ₆ H ₁₀ OS ₂	Natural product	ROS-mediated mitochondrial pathway	[454]
Ginsenoside Rh1	C ₃₆ H ₆₂ O ₉	Natural product	Mitochondrial ROS and ER stress-mediated signaling pathway	[455]
Sulforaphane	C ₆ H ₁₁ N ₀ S ₂	Natural product	ROS-independent pathway involving mitochondrial dysfunction	[456]
Curcumin	C ₂₁ H ₂₀ O ₆	Natural product	Oxidative mitochondrial dysfunction	[457]
Voacamine	C ₄₃ H ₅₂ N ₄ O ₅	Natural product	Disruption of the mitochondrial membrane and potential elicitation of mitochondrial dysfunction	[458]
Resveratrol	C ₁₄ H ₁₂ O ₃	Natural product	Mitochondrial dysfunction	[459]
Celastrol	C ₂₉ H ₃₈ O ₄	Natural product	Mitochondrial dysfunction and apoptosis	[460]
Raddeanin A	C ₄₇ H ₇₆ O ₁₆	Natural product	TDP-43 localization to mitochondria and mtDNA leakage	[461]
CPI-613	C ₂₂ H ₂₈ O ₂ S ₂	Small-molecule metabolic inhibitor	Mitochondrial dysfunction	[462]
IACS-010759	C ₂₅ H ₂₅ F ₃ N ₆ O ₄ S	Small-molecule metabolic inhibitor	Inhibition of complex I of the mitochondrial electron transport chain	[463]
CB-839	C ₂₆ H ₂₄ F ₃ N ₇ O ₃ S	Small-molecule metabolic inhibitor	Inhibition of mitochondrial respiration	[464]
Honokiol	C ₁₈ H ₁₈ O ₂	Natural product	Mitochondrial dysfunction	[465]
Genistein	C ₁₅ H ₁₀ O ₅	Natural product	elevates intracellular ROS generation, decreases mitochondrial membrane potential, and decreases mitochondrial activity	[466]
Magnolol	C ₁₈ H ₁₈ O ₂	Natural product	Accumulation of intracellular ROS and decrease of $\Delta\Psi_m$	[467]
Atovaquone	C ₂₂ H ₁₉ ClO ₃	Natural product	Inhibits mitochondrial respiration and decreases ATP level	[468]
Baicalein	C ₁₅ H ₁₀ O ₅	Natural product	Reduced HIF-1 α expression and downregulation of glycolysis, and mitochondrial biosynthesis	[469]

decline, and mitochondrial permeability transition, revealing the potentials of these drugs in inducing tumor cell apoptosis via mitochondrial pathways.^[61–63] Conventional chemotherapeutic drugs, including 5-fluorouracil (5Fu),^[64] gemcitabine,^[65] and doxorubicin (DOX),^[66] exert antitumor effects by causing mitochondrial damage or dysfunction. However, overexpression of P-glycoprotein (P-gp), which mediates multidrug resistance (MDR), and low tumor selectivities of chemotherapeutic drugs significantly limit the clinical applications of these drugs.^[67]

Therefore, researchers are continuously exploring natural and synthetic small-molecule compounds that target mitochondria (**Table 2**). For example, metformin, clinically used to treat insulin-resistant diabetes, can inhibit the activity of mitochondrial complex I, thus directly exerting antitumor effects by inducing mitochondrial dysfunction^[68] and improving antitumor immunity by promoting CD8 TIL proliferation and IFN- γ release.^[69] Moreover, metformin reduces the side effects of chemotherapeutic drugs by improving mitochondrial function.^[70–71] Mito-metformin, a

mitochondria-targeting analog of metformin, is synthesized by attaching metformin via an alkyl linker with a specific chain length to a triphenylphosphonium cationic moiety (TPP^+). Mito-metformin exhibits higher antitumor efficacy.^[72] AbuEid et al. rationally designed analogs of mito-metformin by incorporating electron-withdrawing trifluoromethyl groups ($\text{pCF}_3\text{-MMe}$ and $\text{mCF}_3\text{-MMe}$) into the ortho and meta positions of the TPP^+ aromatic ring, respectively, and evaluated these analogs. Promising preclinical outcomes have been achieved using these analogs by reducing the electron density on the P atom of the TPP group, thereby enhancing the selectivities of these analogs for cancer cells. Notably, the fluorinated TPP^+ ring also facilitates *in vivo* detection and quantification via ^{19}F -nuclear magnetic resonance spectroscopy. Furthermore, researchers have developed a pMeO-MMe analog of MMe with an electron-rich para-methoxyphenyl group, which enables direct comparison of the influences of electron-withdrawing and electron-donating groups on the electron density of the P atom and subsequent biological effects of TPP^+ -conjugated compounds.^[73] Similarly, modified mitochondria-targeting molecules, such as mito-honokiol, mito-magnolol, mito-atovaquone, and mito-hydroxyurea, exhibit enhanced accumulation in tumor cell mitochondria as compared to that in normal cell mitochondria. These molecules efficiently prevent mitochondrial respiration, induce the production of ROS, activate adenosine monophosphate-activated protein kinase (AMPK) and redox transcription factors, and exhibit antiproliferative functions in cancer cells.^[74]

Growth and metastasis of tumors, hypoxic microenvironments, maintenance of tumor stem cells, and resistance to therapy are accompanied by changes in cellular energy metabolism.^[75–76] Considering the key role of mitochondria in energy metabolism, various mitochondria-targeting drugs, including mitochondrial ETC inhibitors (for instance, metformin), the TCA cycle inhibitor CPI-613, and the mitochondrial glutaminase inhibitor CB-839 (Telaglenastat), have been fabricated for the treatment of tumors.^[50] HSP90 is an oncogenic protein that regulates protein conformation, stability, and degradation, promoting tumor cell growth by enhancing mitochondrial glycolysis, proliferation, and respiration and reducing apoptosis via PKM2.^[77] Novobiocin, a small molecule that inhibits activity at the C-terminus of HSP90 coupled with TPP^+ , exhibits considerable antitumor effects.^[78] Gamitrinib is a small molecule that combines the HSP90 inhibitor 17-AAG with a mitochondria-targeting TPP^+ moiety, inducing acute mitochondrial dysfunction, loss of $\Delta\Psi_m$, and release of cytochrome-c into the cytoplasm of tumor cells. It prevents the development of neuroendocrine- or adenocarcinoma-derived local prostate tumors and metastasis of prostate cancer to abdominal lymph nodes and liver.^[79] A government-funded phase I clinical trial of gamitrinib is currently underway in late-stage cancer patients (ClinicalTrials.gov NCT04827810).^[80] Mitochondrial ClpP protease is responsible for the quality control of mitochondrial proteins as it specifically degrades proteins involved in metabolic processes. Many cancer cells also require overexpressed ClpP to eliminate protein damage caused by ROS and maintain tumor development. Targeting ClpP with small-molecule activators, such as ONC201, to disrupt its function is a promising new strategy in cancer treatment.^[81–82] In summary, these mitochondria-targeting molecules provide

more prospects for targeted mitochondrial therapy in the clinical treatment of tumors.

2.3. Mitochondria-Targeting Probes for Tumor Diagnosis and Treatment

Considering that mitochondria play crucial roles in various cellular processes, for example, energy production, cellular metabolism, and apoptosis, investigating the mitochondria-related biological processes, including changes in the structures, dynamics, and morphologies of mitochondria, mitochondrial metabolism, and mitophagy, is reasonable. Currently, visualization and monitoring techniques are required to elucidate the mitochondrial biology and disease relevance. Multifunctional fluorescent materials, such as small molecules, peptide-conjugated fluorescent moieties, fluorescent proteins, and fluorescent nanomaterials, have been widely developed and applied to label and detect intracellular mitochondrial structures (Table 3). Fluorescence detection has been widely used as a scientific technology for visualizing biological phenomena and systems due to its high sensitivity, excellent selectivity, high signal-to-noise ratio, simplicity, practicality, and real-time detection. Several fluorescent probes, such as MitoTracker Green, MitoTracker Orange, Mito-Tracker Red, and MitoTracker Deep Red, have been developed and commercialized for monitoring mitochondrial or membrane potential.^[83] The mitochondria-targeting enhanced green fluorescent protein (eGFP) and the mitochondrial fluorescent dye MitoTracker Deep Red FM combination can be used for quantitative determination of mitochondrial protein input. In a stable mammalian cell line engineered to express mitochondria-targeting sequence (MTS)-eGFP, an inducible expression system, transient transfection is not necessary, and protein folding stress can be avoided. Additionally, quantitative image analysis using an open-source ImageJ plugin is available.^[84]

Considering the significant role of mitochondria in regulating metabolism, several sensors for mitochondrial metabolites have been constructed. For instance, Li et al. designed a solid-state and water-insoluble fluorophore (HQPQ-B) based on 2-(2'-hydroxyphenyl)-4(3H)-quinazolinone (HPQ) for accurate detection of mitochondrial H_2O_2 . Because of the different mitochondria-targeting abilities of quinoline salts and quinolone, HQPQ is expected to precipitate outside of mitochondria if the probe initially reacts with analytes outside of mitochondria, thus preventing a false positive result (Figure 2a–d).^[85] Li et al. created a piperazine-based mitochondria-immobilized red-emitting fluorescent probe (PMR) for detecting peroxynitrite (ONOO^-), which is mainly produced in mitochondria. This probe contains a piperazine ring in response to alteration in pH, a lipophilic cation for targeting the mitochondrial moiety, and benzyl chloride for immobilizing mitochondrial proteins via thiol groups. Therefore, PMR is a multifunctional molecular probe for imaging both mitochondrial autophagy and ONOO^- (Figure 2e,f).^[86] Luo et al. developed a dual-channel fluorescent probe (NTG) by conjugating a 1,8-naphthalimide derivative with 2-(3-cyano-4,5,5-trimethylfuran-2(5H)-ylidene) malononitrile and 2,4-dinitrobenzenesulfonyl (the responsive site for GSH) for investigating mitochondrial ONOO^- and glutathione (GSH); this probe demonstrated considerable sensitiv-

Table 3. Subcellular structure-targeting probes.

Targeted organelle	Target	Target material	Fluorescent material	Applicability	Reference
Mitochondria	Mitochondrial nitric oxide	Dihydropyridine and triphenylphosphonium (TPP)	BODIPY dye	Detection of exogenous and endogenous nitric oxide in mitochondria	[470]
	Viscosity of mitochondria	meso-CF ₃	BODIPY dye	Analysis of viscosity in mitochondria of living cells	[340]
	HaloTag	JF525-Halo	Rhodamine	Investigation of mitochondrial cristae and morphological changes via super-resolution imaging	[471]
	Selenocysteine	2,4-Dinitrophenyl (DNP) and lipophilic triphenylphosphonium cation (PPh ³⁺)	2,2':6',2"-terpyridine-Tb ³⁺ /Eu ³⁺ mixed complexes	Detection of mitochondrial Sec levels and degree of liver injury	[472]
	Mitochondrial membrane potential and sulfur dioxide		Peptide-conjugated fluorophores	Visual Detection of mitochondrial SO ₂ and membrane potential	[473]
	Protease	Protease-responsive peptide	AIE luminogen	Selective imaging and inhibition of SARS-CoV-2-infected cells	[474]
	Mitochondrial H ₂ O ₂	DNBS thiol detection group	Biocompatible naphthalimide fluorophore and rhodamine B	Mitochondrial thiol detection	[475]
	Mitochondria	Triphenylphosphonium (TPP)	Kaleidolizine	Targeting of mitochondria of live cells	[476]
Nucleus	Mitochondria		Fluorescent nanoparticles	Targeting of mitochondria of live cells	[92]
	Mitochondria		Fluorescent carbon dot	Targeting of mitochondria of live cells	[477]
	Nuclear nitric oxide	Rhodamine spirolactam senses	Hoechst linked to rhodamine spirolactam	Detection of endogenous NO in nuclei of living cells and zebrafishes	[478]
	Viscosity and G-quadruplex DNA	Methyl group of benzothiazole and further N-methylation with iodomethane	Triphenylamine	Imaging of nuclear viscosity and G-quadruplex DNA in living cells	[479]
Endoplasmic reticulum (ER)	Endogenous CYP1A in ER	Methoxy and p-methylbenzene sulfonamide group	Naphthalimide	Imaging of ER stress	[480]
	Viscosity of ER	A methyl sulfonamide moiety	1,8-Naphthalimide	Imaging of ERAP1 activities in living cells	[279]
	Hydroxyl radical ('OH)	Coumarin-3-carboxylic acid (3-CCA)	Pennsylvania Green	Imaging of hydroxyl radical ('OH) in ER	[286]
	Cysteine	p-Toluenesulfonamide	Fluorescein derivative	Imaging of cysteine in ER of living cells	[289]
	Hydrogen sulfide	7-Nitro-1,2,3-benzoxadiazole amine	Naphthalimide fluorophore	Imaging of hydrogen sulfide in the ER	[299]
Lysosome	Hydrogen sulfide	Dinitrobenzenesulfonyl (DNBS) moiety	BODIPY fluorophore	Imaging of H ₂ S in lysosomes of living cells	[337]
	Nitric oxide	Morpholine moiety and 5-amino-2-hydroxy-phenyl	BODIPY dye	Visualizing nitric oxide in lysosomes of living cells	[338]
	Hydrogen peroxide	selenamorpholine	BODIPY fluorophore	Visualizing hydrogen peroxide in lysosomes of living cells	[339]
	Viscosity	Rotatable meso-benzothiazole	BODIPY fluorophore	Imaging of lysosomal viscosity	[340]
	Cholesterol	Dipyrromethene difluoride-cholesterol	BODIPY fluorophore	Visualizing lysosomal cholesterol	[341]
	Fe ⁽²⁺⁾ and H ⁺	Photoinduced electron transfer (PeT) mechanism	BODIPY fluorophore	Detection of Fe ²⁺ and H ⁺ in the lysosomes of living cells	[342]

(Continued)

Table 3. (Continued).

Targeted organelle	Target	Target material	Fluorescent material	Applicability	Reference
Golgi apparatus	Golgi apparatus	Cysteine (Cys) receptor	Neutral red	Golgi apparatus-targeting and in vivo imaging	[385]
	Glutathione		Ratiometric fluorescent probe	Visualizing hydrogen peroxide in Golgi apparatus of living cells	[386]
	Formaldehyde	Phenylsulfonamide moiety and hydrazine	Naphthalimide	Selective sensing of formaldehyde via Golgi apparatus targeting	[387]
	Hypochlorous acid	Dimethylthiocarbamate	1,8-Naphthalimide	Quantification of hypochlorous acid in Golgi apparatus	[481]
Cell membrane	Viscosity of cell membrane	Triphenylamine unit	Acetonitrile pyridinium	Selective visualization of tumor and normal cells	[402]
	Polarity of tumor cell membrane	Coumarin	Coumarin	Selective visualization of tumor and normal cells	[403]
	Polarity of tumor cell membrane	Quaternary ammonium groups	Tetrahydroquinoxaline coumarin amide	Selective visualization of tumor and normal cells	[405]

ties and selectivities for the monitoring of GSH and ONOO⁻ (Figure 2g–i).^[87]

In recent years, the application of nanotechnology in mitochondrial targeting and imaging has attracted significant attention due to the effectiveness, versatility, and multifunctionality

of nanotechnology.^[88,89] Nanomaterials are valuable tools for the precise diagnosis and treatment of cancer via mitochondrial targeting owing to their abilities to load different materials including drugs, fluorescent dyes, responsive units for analytes, gene intervention vectors, and motifs that target mitochondria.^[83,90–92]

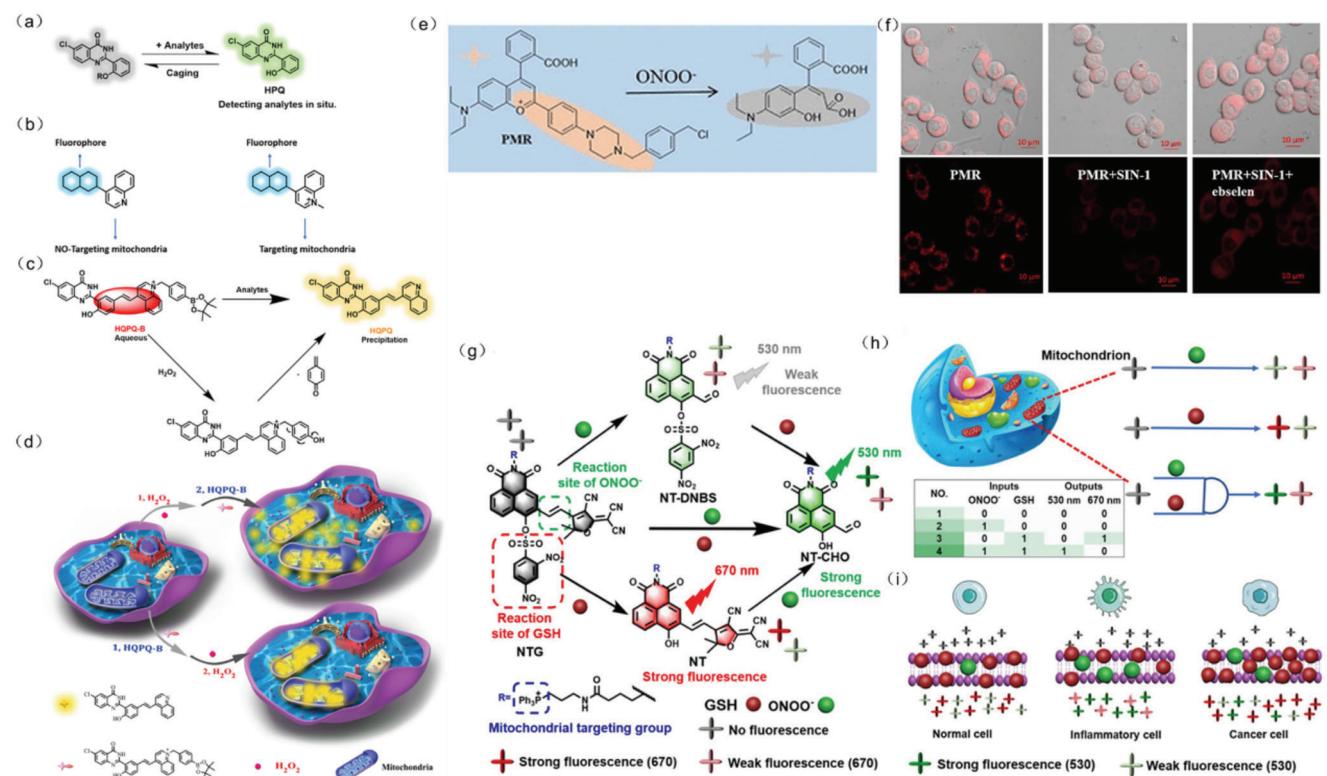


Figure 2. Mitochondria-targeting probes for mitochondrial metabolite imaging. a) 2-(2'-Hydroxyphenyl)-4(3H)-quinazolinone (HPQ) for imaging active species in situ. b) Targeting capacities of quinoline salt and quinoline. c) Formation of quinoline salts by modification of quinoline on HPQ (HQPQ-B). d) Accurate detection of mitochondrial analytes. Reproduced with permission.^[85] Copyright 2021, American Chemical Society. e) Schematic of synthetic PMR. f) Imaging of exogenous ONOO⁻ in living cells.^[86] Copyright 2022, American Chemical Society. g) Proposed mechanism for the reaction of the probe with GSH and ONOO⁻. h) Programmed operation of the input circuits. i) Strategy for the discrimination of normal, inflammatory, and cancer cells by the detection of GSH and ONOO⁻ in mitochondria. Reproduced with permission.^[87] Copyright 2022, American Chemical Society.

An example of nanomaterials that are used for nanotechnology-based mitochondrial targeting and imaging is therapeutic Pt(IV)-NPs, which self-assemble in a 1:1 molecular ratio of cyclodextrin-functionalized IR780 and biotinylated Pt(IV) prodrugs. The small molecule dye IR780 in the NPs acts as a mitochondria-targeting ligand, facilitating the relocalization and release of CDDP in mitochondria. Functional assays have revealed that Pt(IV)-NPs substantially induce mitochondrial dysfunction, thereby reducing cisplatin resistance of A549R cancer cells.^[93] Mitochondrial dysfunctions, indicated by mitochondrial ROS, H₂O₂, GSH, and pH fluctuations in the tumor microenvironment (TME), are hallmarks of tumor development.^[94–96] Development of highly sensitive probes that can recognize and differentiate the unique physiological microenvironments of cancer cells is promising for early cancer diagnosis.^[97] For instance, porphyrin–polyethylene glycol (PEG) nanocomplexes (PPNs) are a size-controllable and dual tumor-mitochondria-targeting theranostic nanoplatform. As measured by PET imaging tracing, PPNs gained enhanced tumor accumulation and satisfactory tumor-to-muscle ratio. Furthermore, ¹⁷⁷Lu-PPNs can be effectively taken up by tumor cells and mitochondria, which further considerably enhances the efficacies of radiation therapy and/or PDT.^[98] The mitochondria-targeted approach also enables real-time monitoring of drug delivery and release during cancer treatment.^[99,100]

Biological peptides and proteins are vital resources for developing mitochondrial imaging tools. Mitochondria-penetrating peptides (MPPs), composed of six residues including cationic arginine and the artificial amino acid cyclohexylalanine, are mitochondrial molecular carriers that target the mitochondrial matrix.^[101] Peptide-based delivery strategies, characterized by their ease of synthesis and tunability, facilitate covalent linkage of mitochondria-targeting peptides to targeted therapeutic agents, enhancing drug properties and providing insights into mitochondrial biology for potential therapeutic advancements.^[102] Jeena et al. designed a mitochondria-penetrating tripeptide containing diphenylalanine units, termed Mito-FF, and Mito-FF exhibited mitochondria-targeting ability. The short peptide amphiphile Mito-FF co-assembled with its mirror in cells and contributed to severe dysfunctions of mitochondria.^[103] Nevertheless, using engineered fluorescent proteins, real-time visualization of proteins of interest with high resolution and sensitivity has been realized. mt-Keima is an extensively used fluorescence imaging technique for monitoring mitochondrial autophagy in vitro and in vivo.^[104] Further applications of mt-Keima can distinguish whether mitochondria are in the cytoplasm or in acidic lysosomes, thus enabling the analysis of mitochondrial autophagy in cells.^[105] Moreover, the mt-Keima transgenic mice were developed, making it possible to measure mitophagy in vivo.^[106] NAD(P)H:quinone oxidoreductase-1 (NQO1) is a flavoprotein that is overexpressed in multiple tumor cells and is an effective biomarker for early cancer diagnosis. Establishing a fast, selective, and sensitive cell-level NQO1-monitoring method would significantly promote clinical cancer diagnosis. Yuan et al. constructed a rapid NQO1-responsive fluorescent probe, SYZ-30. Two fluorophores, including quinone and 7-nitro-2,1,3-benzoxadiazole (NBD), were contained in this probe, making it possible to selectively and rapidly detect NQO1 alteration.^[107] Additionally, Wang et al. have designed and synthesized a fluorescent quinolinium derivative, QUCO-1. Dual roles of this probe were identified as it can not

only function as a mitochondrial probe, but also can effectively induce severe mitochondrial dysfunction and OXPHOS inhibition in cancer cells.^[108]

2.4. Mitochondria-Targeting Materials for Tumor Treatment

Subcellular mitochondria-targeting materials have attracted interest in cancer treatment due to their combined structural targeting, drug delivery, and imaging abilities.^[109–110] By developing mitochondriotropic particulate carriers, which selectively transport drugs or small molecules to mitochondria, the cellular and mitochondrial barriers of tumor cells can potentially be overcome.^[111] Recently, NPs based on liposomes, metal oxides, Au NPs, dendrons, C nanotubes (CNTs), and amphiphilic copolymers have been engineered to target mitochondria and have emerged as eminent candidates for efficient drug delivery.^[112] Targeting mitochondria using nanoformulations offers numerous advantages owing to improved water solubilities, enhanced activities, and reduced systemic toxicities of nanoformulations. Additionally, these formulations demonstrate advantages such as prolonged circulation times, higher concentrations at tumor sites, delivery of multiple synergistic drugs, controlled drug release at tumor sites via stimulus-sensitive delivery systems (for example, pH-, temperature-, and enzyme-sensitive nanoformulations), abilities to overcome MDR, and high therapeutic efficacies. Utilization of numerous nanoformulations to target organelles has transformed the therapeutic approaches to several diseases including cancer.^[113]

2.4.1. Mitochondria-Targeting Liposomes in Cancer Treatment

In 1964, Alec Bangham discovered the structures of liposomes, which are vesicular structures composed of one or more bilayer phospholipid membranes and an aqueous cavity.^[114] Liposomes exhibit low toxicities, high biocompatibilities, biodegradabilities, and the abilities to load both hydrophilic and hydrophobic drugs. Thus, liposomes are excellent candidates as drug delivery carriers. Liposomal formulation of DOX is the first FDA-approved class of nanomedicines.^[115]

Triphenylphosphine (TPP) is one of the most widely used mitochondria-targeting lipophilic cationic ligands.^[116] Artemisinin is an effective antimalarial drug, and artemisinin and its derivatives inhibit tumor growth by inducing mechanisms such as mitochondrial autophagy in tumor cells.^[117–118] However, the lack of tumor-targeting abilities of artemisinin-like drugs limits their application in cancer treatment. Researchers have fabricated a GSH-sensitive artemisinin prodrug, TPP-SS-ATS, based on TPP and further developed a liposome, TPP-SS-ATS-LS called TPP-SS-ATS-LS. Finally, this functional material can dually target tumor cells and tumor cell mitochondria (Figure 3a). The corresponding experiments revealed that the tumor growth inhibition ratio (TGI) of 30 mg kg⁻¹ artemisinin was 37.7%, whereas the TGI of the same dosage of TPP-SS-ATS-LS was nearly 56.4% in BC orthotopically implanted mice (Figure 3b). Intraperitoneally injected TPP-SS-ATS-LS accumulated at the tumor site after 24–60 h of administration (Figure 3c), and TPP-SS-ATS-LS treatment caused no evident

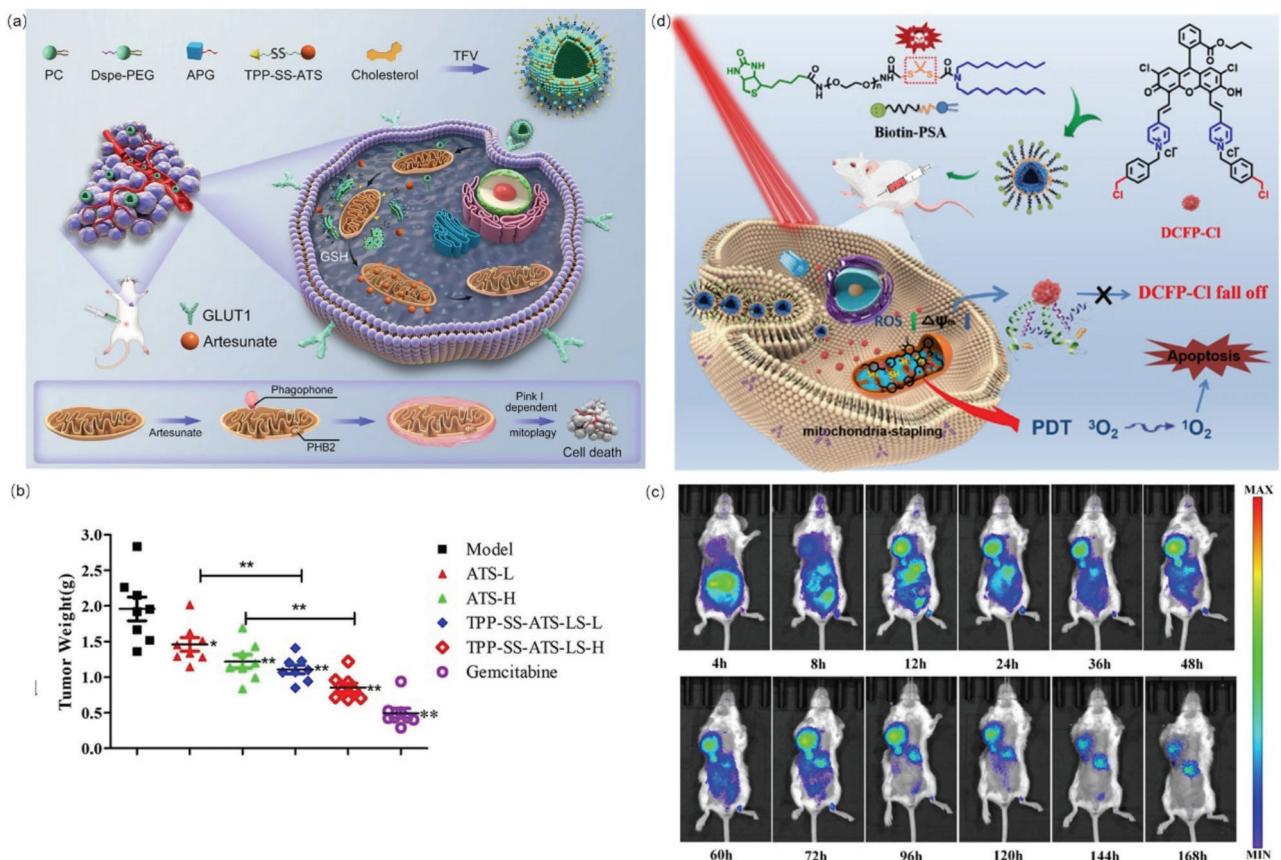


Figure 3. a) Schematic of TPP-SS-ATS-LS. b) Tumor volume changes in each group during the experiment. The L group represents 15 mg kg^{-1} dosage, and the H group denotes 30 mg kg^{-1} dosage. c) In vivo fluorescence imaging of 4T1 tumor-bearing Balb/c mice after intraperitoneal injection with DiR-TPP-SS-ATS-LS. Reproduced under the terms of Creative Commons Attribution 4.0 International License.^[119] Copyright 2022, The Authors, published by Springer Nature. (d) Strategy and mechanism of Biotin-PSA@DCFPCl for enhancing antitumor efficacy in PDT. Reproduced with permission.^[128] Copyright 2022, American Chemical Society.

hepatic or kidney toxicity in mice. In terms of the mechanism, TPP-SS-ATS-LS downregulated the expression of PHB2 and inhibited tumor cell proliferation via the PTEN-induced kinase 1-dependent mitochondrial autophagy mechanism. These findings afford a new strategy for enhancing the antitumor efficacies of artemisinin-like drugs.^[119] DOX is a broad-spectrum anticancer antibiotic; nevertheless, its lack of specificity results in severe systemic toxicity, limiting its long-term clinical application.^[120] Chen et al. improved the mitochondrial delivery efficiency of DOX by coupling glycyrrhetic acid (GA), TPP, and DOX. They encapsulated the GA-DOX-TPP (GDT) mitochondria-targeting prodrug in cationic liposomes (CLs) and constructed a layered delivery system, HA-GDT-Lip, by coating the CL surface with anionic polysaccharide hyaluronic acid (HA). With enhanced permeability and retention effects, HA-GDT-Lip has ideal accumulation in tumor sites and achieved CD44 receptor-mediated tumor cell-specific internalization. The study indicated that HA-GDT-Lip induced mitochondrial permeability transition pore opening, thereby accelerating apoptosis of tumor cells both in vitro and in vivo. Additionally, HA-GDT-Lip demonstrated outstanding antitumor activity and in vivo safety in tumor-bearing nude mice. This HA-modified lipid NP-based mitochondria-targeting layered delivery system reduces the side

effects of chemotherapeutic drugs and improves antitumor efficacies of these drugs.^[121]

Compared to traditional radiation and chemotherapy, tumor PDT offers minimally invasive/noninvasive targeted treatment and high applicability. Researchers have achieved targeted mitochondrial delivery by attaching TPP⁺ to the PS protoporphyrin IX (TPPP), which induced PDT via the oxidation of mitochondria and consequent apoptosis of cells.^[122] The natural cyclopeptide RA-XII was selected as an anti-colon cancer chemotherapeutic agent.^[123,124] pH-sensitive liposomes were used to load RA-XII and TPP-modified porphyrin, and HA was coated on the surfaces of the liposomes to enhance the colon tumor-targeting abilities of the liposomes. Based on this liposome NP, a multistage responsive intelligent nanomedicine platform with both chemotherapy and PDT functions was developed (RA/TPPP-Lip). RA/TPPP-Lip can trigger the precise release of RA-XII and TPP in colon cancer cells and exhibits lower cytotoxicity, adequate bioavailability, high hematological safety, and in vivo biocompatibility. Under laser irradiation, TPP and RA-XII acted together to activate apoptosis in tumor tissues. This new cancer-targeted nanomedicine platform provides a novel strategy for precise combination therapy.^[122] Mitochondria-targeting PDT (Mt-PDT) has emerged as a promising strategy for

enhancing the efficacy of PDT in cancer treatment by stimulating apoptotic cascade signal amplification in mitochondria.^[125–126] However, the use of cationic PSs in mitochondria-targeting liposomes for PDT is limited by the tendencies of these PSs to leak from mitochondria, thereby reducing the treatment efficacy. To address this issue, researchers have constructed new types of PSs that can target and stably anchor to mitochondria.^[127] A mitochondria-stapling PSs, DCFP-Cl, has been designed and synthesized, and a liposome-based nanophotosensitizer, biotin-prostate-specific antigen (PSA)@DCFP-Cl, has been developed. DCFP-Cl has two benzyl chloride subunits that can covalently react with the sulfhydryl groups of peptides and proteins in mitochondria, anchoring DCFP-Cl to the mitochondria without falloff effects. DCFP-Cl and the amphiphilic monomer biotin-PSA self-assemble to form a liposomal nanosystem. The liposome-based nanophotosensitizer exhibits a high PDT efficiency ($IC_{50} = 0.98 \mu\text{M}$) under 630 nm light irradiation. The results of mouse experiments also demonstrated outstanding antitumor PDT activity of the liposome-based nanophotosensitizer^[127] (Figure 3d).

Hybridization of liposomes with NPs is a significant strategy for designing drug delivery systems that combine the advantages of both liposomes and NPs.^[128] Researchers have designed mitochondria-targeting PSs (PQC NFs) that can be retained within tumor sites *in vivo* for up to 10 days.^[129] Nevertheless, this nanomaterial cannot be administered via intravenous injection, thus limiting its clinical application. Consequently, researchers have further assembled a PS (PQC) with liposomes to develop a mitochondria-targeting *in situ* glioma nanoplateform (LPHNPs) for imaging and therapy. LPHNPs integrate the advantages of both materials: they can be intravenously administered and possess excellent loading capacities, low systemic toxicities, high biocompatibilities, high stabilities, mitochondria-targeting abilities, fluorescence imaging abilities, and photosensitivities. After being administered to tumor-bearing mice, LPHNPs accumulated at the tumor site after 2 h of injection and remained there for at least 48 h. Laser-activated LPHNPs substantially prevented tumor growth and prolonged overall survival of the mice (median survival > 60 days), and three mice in the LPHNPs plus laser group survived beyond 60 days. Sonodynamic therapy is another strategy used for cancer diagnosis and treatment due to its high tissue permeability, minimal invasiveness, and low cost.^[130] IR780 is a PS with high fluorescence quantum yield, high ultrasound-induced ROS production, and high tumor accumulation ability. However, it cannot actively target the mitochondria where it can better exert its efficiency. Although the GDH1 inhibitor R162 demonstrates anticancer properties, its efficacy is low owing to the absence of mitochondria-targeting ability. Researchers have encapsulated R162 and IR780 in mitochondria-targeting liposomes to form a multifunctional nanocarrier, Mito@Lip/R162/IR780 (MLipRIR NPs), which can efficiently target and enter the tumor mitochondria to realize antitumor immunity.^[131]

2.4.2. Mitochondria-Targeting Metal NPs

A range of metal NPs, including iron oxide, Au, Ag, zinc oxide, and copper oxide NPs, have been fabricated and exam-

ined for clinical applications. Compared to liposomes and other carriers, metal NPs exhibit photoelectric properties related to surface plasmon resonance, which can broaden their clinical applications.^[132–133] Functional modifications, such as via chemical covalent crosslinking of drugs or probes, of metal NPs can also enable them to serve as drug delivery systems.^[134] As one of the earliest and most stable NPs investigated to date, Au NPs have been widely used in biomedical applications due to their ease of synthesis and diverse surface modification characteristics.^[135]

Developing targeted radiosensitizers is one of the most important strategies to improve the precision and reduce the side effects of cancer radiotherapy on normal tissues. Owing to the unique advantages originating from the structure–property correlations of atomically precise clusters, atomically precise Au clusters have become extensively attractive functional nanomaterials.^[136–137] Thus, atomically precise Au clusters are attractive candidates for high-Z element-based radiosensitizers. Hua et al. have designed water-soluble, mitochondria-targeting atomically precise $\text{Au}_{25}(\text{S-TPP})_{18}$ clusters (TPP-SNa = sodium 3-(triphenylphosphonio) propane-1-thiolate bromide) by introducing TPP⁺ into the ligand (Figure 4a–c). Compared with $\text{Au}_{25}(\text{SG})_{18}$ clusters (SG = GSH), $\text{Au}_{25}(\text{S-TPP})_{18}$ demonstrates higher mitochondria-targeting ability and radiosensitivity, TrxR inhibition, and ROS generation, thus causing a stronger antitumor immune response (Figure 4d). Furthermore, using the combination of chemotherapy based on this Au nanocluster and immune therapy based on CTLA-4 checkpoint blockade, effective distant antitumor effects can be achieved.^[138] Au NPs can also function as PS carriers for PDT. Application of *in situ* biosynthesized fluorescent Au nanoclusters has become a potential strategy for precise targeted cancer cell imaging and tumor treatment due to the excellent biocompatibilities and ultrasmall sizes suitable for labeling tumors of these nanoclusters.^[139–140] According to this strategy, Xiong et al. prepared mitochondria-targeting aptamer–porphyrin conjugates (ApPCs) by covalently linking porphyrin PSs to mitochondria-targeting aptamers. Then, using ApPCs as a synthetic template, fluorescent Au NCs-ApPCs were specifically and *in situ* biosynthesized in the TME. *In vivo* experiments verified long-term tumor localizations and low biotoxicities of Au NCs-ApPCs. Under 660 nm laser irradiation, the Au NC-ApPC component induced tumor cell apoptosis via a mitochondria-targeting PDT effect.^[141]

Iron oxide NPs are another type of metal NPs that have exhibited promise in cancer treatment. Iron oxide NPs possess several advantages, for instance, facile preparation, superparamagnetism, high magnetic heat sensitivities, and high magnetization rates.^[142–144] Sood et al. synthesized mitochondria-targeting Au-coated iron oxide NPs (GNPs) modified with α -ketoglutaric acid (Fe:Au = 1:7) (Figure 4e). Moreover, the researchers loaded the chemotherapeutic drug *N*-(4-hydroxyphenyl) retinamide (4-HPR) into GNPs, achieving a drug loading efficiency of 8.5 wt% and inducing tumor cell death. The application of GNP at 5 Gy gamma radiation dose significantly reduced the percent cell viabilities of hepatocellular carcinoma cells. *In vivo* biodistribution studies indicated that the GNPs demonstrated systemic clearance after initial accumulation, and the liver reported maximum retentions of GNPs as compared to those of the spleen and kidney (Figure 4f–h).^[145]

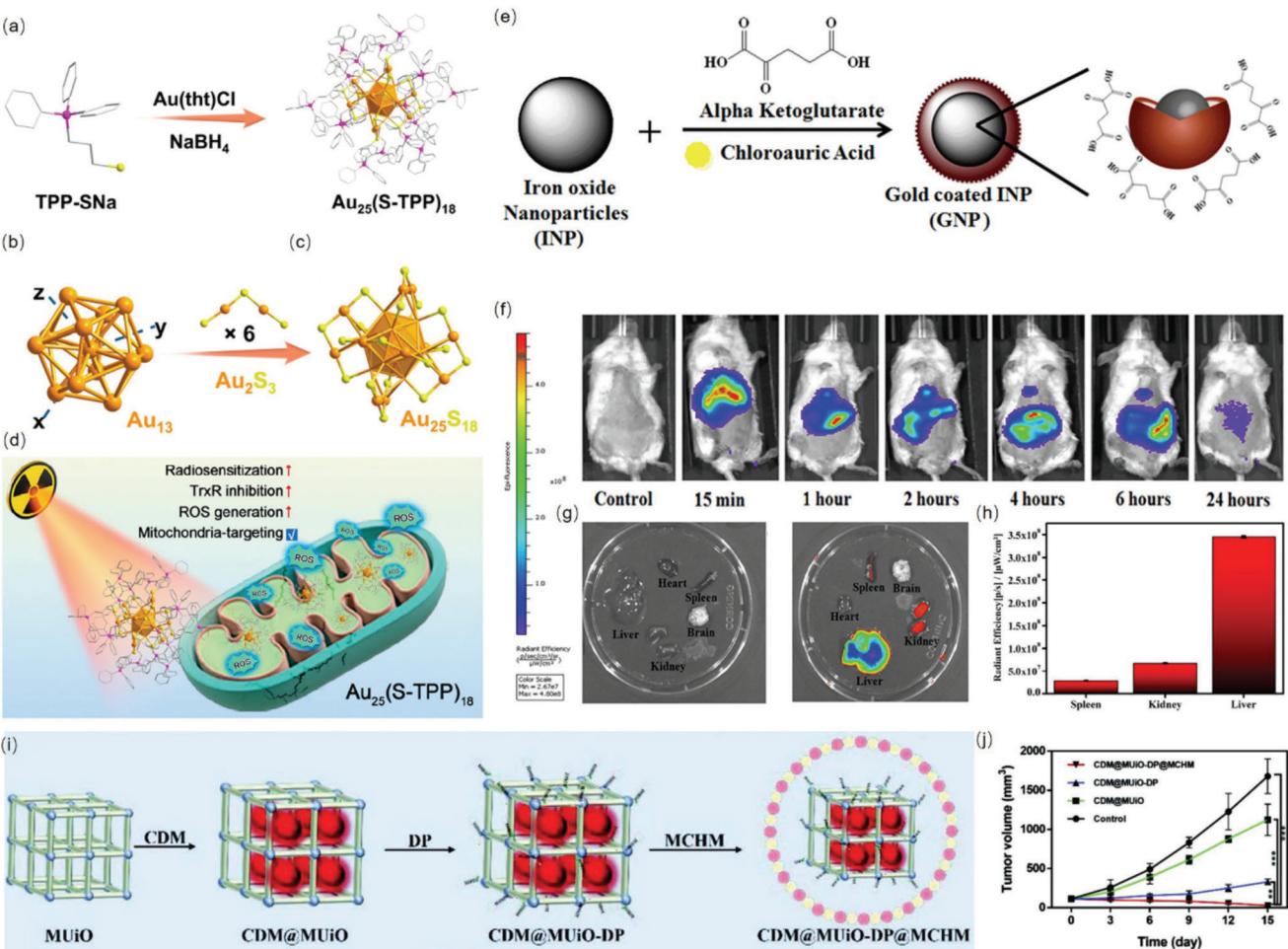


Figure 4. (a–c) Synthetic route for $\text{Au}_{25}(\text{S-TPP})_{18}$. (d) Mechanism of mitochondrial targeting by $\text{Au}_{25}(\text{S-TPP})_{18}$ in tumor cells. Reproduced with permission.^[138] Copyright 2023, American Chemical Society. (e) Schematic of the synthesis of GNP. (f–h) Whole body biodistribution of indocyanine green-tagged GNP in the spleen, kidney, and liver of Balb/C mice. Reproduced with permission.^[145] Copyright 2021, Elsevier B.V. (i) Schematic of the preparation of CDM@MUiO-DP@MCHM. (j) Changes in the tumor volume of tumor-bearing mice after various treatments. Reproduced with permission.^[148] Copyright 2023, Wiley-VCH GmbH.

2.4.3. Mitochondria-Targeting Metal-Organic Frameworks

Metal–organic frameworks (MOFs) belong to a group of hybrid crystalline porous materials composed of organic ligands and metal/metal clusters. MOFs exhibit superior properties, such as high porosities, adjustable porosities, high surface areas, and modifiable functionalities and structures, and are attracting extensive attention in cancer treatment.^[146–147] Li et al. established a macrophage–cancer hybrid membrane (MCHM) derived from macrophage cells and MCF-7 cells and coated the MCHM on MUiO-66. They loaded the MOFs with miRNA biomarker detection probes for cancer diagnosis and a mitochondrial Cu depletion moiety (CDM) as an anticancer agent, resulting in the functional NPs CDM@MUiO-DP@MCHM. After internalization of CDM@MUiO-DP@MCHM by the cells, miRNA-21-mediated fluorescence resonance energy transfer (FRET) could be effectively utilized for cancer diagnosis, whereas CDM-induced cancer cell apoptosis. When injected into nude mice bearing tumors, CDM@MUiO-DP@MCHM demonstrated

high homing targeting, immune escape, and anticancer abilities (Figure 4i,j).^[148] Zhou et al. designed a mitochondrial-targeting MOFs, namely the ZrMOF-PEG-TPP@DOX NCs. This functional material was loaded by porous zirconium metal-organic framework nanocubes (ZrMOF NCs) and further modified with PEG. Thus, enhanced bioavailability and excellent heating effects were achieved due to the increased collisions of ions in the micropores and preferential mitochondrial aggregation.^[149] Additionally, Ni et al. developed Hf-DBB-Ru, a nanoscale MOF (nMOF), for enhancing the efficacy of PDT by targeting mitochondria. Hydroxyl radicals and singlet oxygen were efficiently generated from the Hf-DBB-Ru following X-ray irradiation, thus enhancing radiotherapy (RT) and enabling radiodynamic therapy (RDT). Moreover, apoptosis of cancer cells was initiated after mitochondria-targeted RT-RDT depolarization, leading to significant regression of colorectal tumors in mouse models.^[150] Impressively, Peng et al. have recently designed autonomous MOF nanorobots, namely the ZIF-67@DOX-TPP nanorobots. ZIF-67@DOX-TPP can decompose bioavailable hydrogen

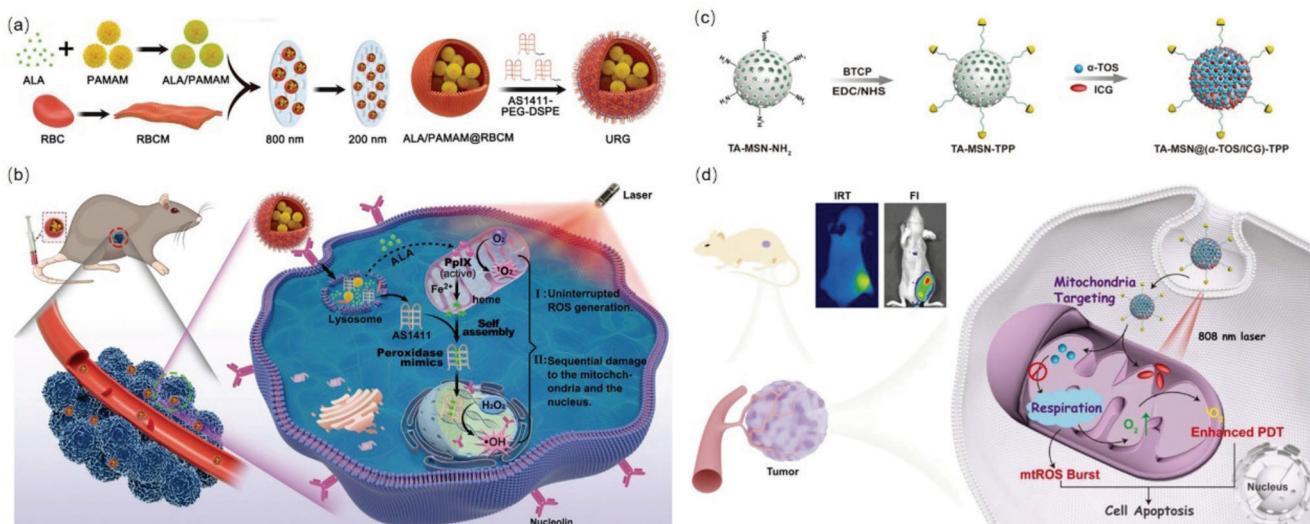


Figure 5. (a) Schematic of the synthesis of URG. (b) Mechanism of augmented free radical therapy of URG for antitumor activity. Reproduced with permission.^[155] Copyright 2022, Wiley-VCH GmbH. (c) Schematic of the fabrication of TA-MSN@(α -TOS/ICG)-TPP. d) Schematic of mitochondrial targeting by TA-MSN@(α -TOS/ICG)-TPP nanoparticles in tumor tissue. Reproduced with permission.^[164] Copyright 2021, Wiley-VCH GmbH.

peroxide overexpressed inside the tumor cells and then generate effective intracellular mitochondriotropic movement with the help of triphenylphosphonium (TPP) cation. Thus, significant antitumor effects are achieved by this nanorobot by inducing mitochondria-mediated apoptosis and mitochondrial dysregulation.^[151]

2.4.4. Mitochondria-Targeting Dendrimer Nanoplatforms

Dendrimers are a unique class of nanomaterials with three-dimensional branching structures consisting of an initial core, repetitive branching units, and terminal groups connected to the outermost repetitive branching units.^[152] Dendrimers exhibit desirable features, such as facile surface modifications, excellent stabilities, and biocompatibilities, and have been extensively explored in the field of biomedicine.^[152] Cheng et al. fabricated a novel TME-responsive core-shell tecto dendrimer (CSTD). Though loading the dendrimer with Cu ions and the chemotherapeutic drug, the synthetic novel material CSTD-Cu(II)@DSF enhanced tumor magnetic resonance (MR) imaging (MRI) and accelerated tumor clearance by inducing cupropotosis and mitochondrial dysfunction.^[153] Yunqi et al. developed a multifunctional nanoplatform with a size of 210 nm, loaded it with P dendrimer-copper(II) complexes (1G3-Cu) and toyocamycin (Toy). Cancer cell membranes were further coated outside the nanoplatforms. The designed GCT@CM NPs induced mitochondrial dysfunction, amplified endoplasmic reticulum stress, and achieved marked tumor growth inhibition.^[154]

5-Aminolevulinic acid (ALA), the precursor of the endogenous PS protoporphyrin IX (PpIX), induces $^1\text{O}_2$ generation in mitochondria for tumor ablation. Although free radical therapy based on ALA has been approved by the FDA for clinical tumor treatment, the discontinuity of ALA-mediated free radical production has limited its clinical efficiency.^[155] Therefore, Shi et al. took advantage of a recycling strategy and constructed an intracellular

self-assembly-driven uninterrupted ROS generator (URG). ALA was loaded into amino-terminated polyamidoamine (PAMAM) dendrimers, which were then enclosed by red blood CM (RBCM) vesicles to form ALA/PAMAM@RBCM. The material surface was further modified with G-quadruplex-structured AS1411, endowing URG with tumor-targeting ability. AS1411G catalyzed the conversion of ineffective heme to functional enzymes, leading to uninterrupted generation of $^1\text{O}_2-\bullet\text{OH}$. Overall, URG enhanced the free radical-mediated antitumor effects^[155] (Figure 5a,b).

Development of dendritic stable NPs has gained attention as these NPs exhibit integrated advantages of both NPs and dendritic polymers. In PDT, insufficient light penetration will affect the efficiencies of PSs. Upconversion NPs (UCNPs) can transform NIR light to ultraviolet (UV) or visible (vis) light, achieving higher tissue penetration depths. Accordingly, researchers have designed an organic-inorganic nanocomposite system with mitochondria-targeting ability. A multifunctional nanocarrier, UCNPs@G4/Ce6/CAT-CTPP, has been synthesized using a novel thiol-ene and azide-acetylene click reaction route to connect the original oleic acid ligands and dendritic polymers. The hydrophobic PS chlorin e6 (Ce6 upconversion and MR dual-mode bioimaging) and hydrophilic catalase (CTA) can be simultaneously loaded into these UCNPs. This multifunctional NP system effectively enhanced the PDT efficacy while achieving upconversion and MR dual-mode bioimaging.^[156]

2.4.5. Mitochondria-Targeting CNTs

CNTs are tube-shaped nanomaterials comprising C atoms that form a honeycomb nanoscale structure. CNTs can be classified as single-walled CNTs (SWNTs) and multiwalled CNTs (MWCNTs) depending on the number of C layers. CNTs demonstrate various excellent properties such as the ability to penetrate cells due to their specific tubular structures, diverse surface modification

abilities, thermal conductivities, and optical properties, rendering them potential tools for tumor diagnosis and drug delivery in the field of cancer treatment.^[157] SWNTs are exceptional quasi-one-dimensional materials that can autonomously enter cells. Zhou et al. have discovered that SWNTs can enter cells and label mitochondria owing to their mitochondrial transmembrane sites. Further research has revealed that SWNTs can more effectively accumulate in cancer cell mitochondria due to the high $\Delta\Psi_m$ in tumor cells and selectively destroy cancer cell mitochondria under 980 nm laser irradiation, realizing targeted photothermal therapy (PTT) of tumors.^[158] Researchers have also applied SWNTs to photoacoustic therapy. Under 1064 nm pulsed laser irradiation, 79.4% cancer cells with intracellular SWNTs killed 79.4% of cancer cells within 20 s, whereas normal cells remained with an alive rate of 82.3%.^[159] Yoong et al. utilized mitochondria-targeting fluorescent rhodamine 110 to functionalize MWCNTs by constructing MWCNT-Rho with outstanding mitochondria-targeting ability. By co-encapsulating the chemo-potentiator 3-bromopyruvate (BP) and Pt (IV) prodrug (PtBz) in MWCNT-Rho, MWCNT-Rho (PtBz + BP) was obtained. MWCNT-Rho (PtBz + BP) actively targeted cancer cell mitochondria, exhibiting superior efficacy as compared to those of PtBz-free drugs.^[160]

2.4.6. Mitochondria-Targeting Mesoporous Silica NPs (MSNs)

MSNs are solid entities with surface abdominal pores that were discovered by Mobil researchers for the first time. The term “mesoporous” in MSNs describes the pore size.^[161] Unlike liposomes, Au NPs, and other materials, MSNs demonstrate unique core–shell structures. MSNs exhibit high surface areas, typically exceeding $1000\text{ m}^2\text{ g}^{-1}$, which enables multiple independent modifications of pore sizes and surface chemistry, facilitating the loading of numerous drugs.^[162] The excellent thermal stabilities, biocompatibilities, size and shape control-driven multifunctionalities, and multiple modifications for mitochondria-targeting render MSNs highly promising in drug delivery.^[161]

MSNs have been widely explored as anticancer drug carriers. Nevertheless, their application is hindered by many challenges including the absence of targeting ability and high risk of hemolysis. Lee et al. developed DOX@MSNs-man-g-poly(acrylic acid) (PAA) coated with mannose-grafted PAA copolymer and loaded with the chemotherapeutic drug DOX. At a DOX concentration of 2 mg mL^{-1} , both DOX@MSNs and bare MSNs demonstrated $>20\%$ hemolysis, whereas DOX@MSNs-man-g-PAA exhibited negligible hemolysis (only 3.10%). Mannose receptor-mediated endocytosis significantly improved the uptake of DOX@MSN-man-g-PAA by BC cells, demonstrating outstanding tumor suppression activity in mice implanted with MDA-MB-231 cells.^[163] Dong et al. prepared TPP-modified MSNs (trimethylammonium (TA)-MSN-TPP) and loaded α -tocopherol succinate (TOS) and indocyanine green (ICG) into it via strong electrostatic interactions between drug molecules and TA groups in the nanopore. TA-MSN@(α -TOS/ICG)-TPP can block the mitochondrial respiration chain and reduce innate O consumption to induce endogenous mtROS accumulation, which exhibited better PDT performance in a tumor-bearing mouse model^[164] (Figure 5c,d). Naz et al. developed an enzyme-responsive, multistage-targeted MSN

drug delivery system (MSN-DPH) that achieved mitochondrial targeting via TPP modification and tumor targeting by molecular HA modification and carried the anticancer drug DOX. Based on the abovementioned design, MSN-DPH realized targeted uptake by cancer cells via CD44 receptor-mediated endocytosis and ultimately localized to mitochondrial sub-organelles. Under the degradation of overexpressed hyaluronidase in cancer cells, MSN-DPH responsively released the chemotherapeutic agent DOX.^[165]

2.4.7. Mitochondria-Targeting C Quantum Dots (QDs) (CQDs)

C dots (CDs) were discovered in 2004 and are defined as a type of zero-dimensional C NPs with sizes smaller than 10 nm and crystal lattice parameters of 0.34 nm.^[166] CDs demonstrate multiple advantages such as appropriate biocompatibilities due to the presence of C and adequate bioimaging abilities owing to their small sizes. Tian et al. used three pentacyclic triterpenoids (PTs), namely, GA, ursolic acid, and oleanolic acid, with anti-cancer effects as precursors to fabricate novel CDs, PT-CDs, via simple microwave synthesis. PT-CDs efficiently localized in mitochondria. Functionally, the researchers demonstrated that all three CDs retained their active surface groups and could produce green fluorescence. In cancer cells, PT-CDs induced cell death via three pathways (that is, apoptosis, ferroptosis, and autophagy), which are inherited from 3 raw materials but with greater efficiency. Studies on HCT116 tumor-bearing nude mice indicated antitumor properties and low systemic toxicities of PT-CDs in vivo.^[167] Cilingir et al. synthesized metformin-derived CDs (Met-CDs) using a microwave-assisted method which acquire low toxicity in nontumor cells and prominent biocompatibility in tumor cells. Other properties, such as living cell bioimaging, tumor cell membrane penetration, and accumulation in the nucleus and mitochondria were found and comprehensively characterized them using UV-vis spectroscopy, photoluminescence (PL) spectroscopy, Fourier transform infrared (FTIR) spectroscopy, X-ray photoelectron spectroscopy (XPS), atomic force microscopy (AFM), and transmission electron microscopy (TEM).^[168] Qi et al. designed an intelligent hybrid plasmonic nanoprobe, denoted as CD-Ag/Au nanoshells (NSs), using CDs as surface modifiers of porous Ag/Au bimetallic NSs. Assembling CD-Ag/Au NSs with mitochondria- and nuclear-targeting peptides can further confer organelle-targeting abilities to CD-Ag/Au NSs. Due to the appropriate light absorption abilities of C nanomaterials, CD-Ag/Au hybrid NSs exhibited better photothermal conversion abilities and biocompatibilities than those of parent p-Ag/Au hybrid NSs.^[169]

2.4.8. Mitochondria-Targeting Amphiphilic Copolymers

Amphiphilic copolymers, formed by the combination of hydrophobic and hydrophilic segments with one or more hydrophilic and hydrophobic monomer units, respectively, have attracted extensive attention of drug developers because of their better transport stabilities, structural versatilities, tunable drug release abilities, and low systemic toxicities.^[170–171] Yang et al. encapsulated a mitochondria-targeting NIR-absorbing PS (IR-FE-TPP) (IR-FE modified with four TPPs) in a dual-responsive

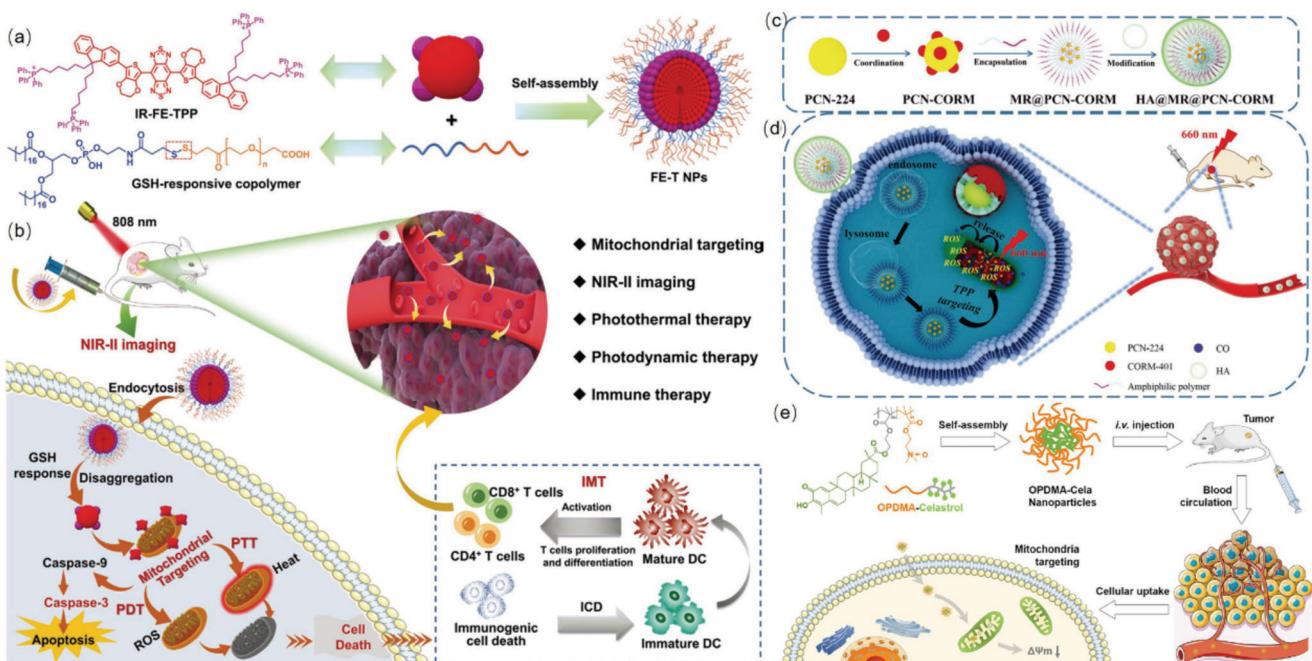


Figure 6. a) Schematic of the synthesis of FE-T NPs. b) Mechanistic diagram of FE-T NP antitumor therapy via NIR-II imaging-guided mitochondrial targeting. Reproduced with permission.^[172] Copyright 2023, Wiley-VCH GmbH. c) Schematic of the composition of HA@MR@PCN-CORM. d) Schematic of the transport of HA@MR@PCN-CORM in tumor cells. Reproduced with permission.^[173] Copyright 2023, Wiley-VCH GmbH. e) Schematic of the OPDMA-Cela conjugate and its journey in vivo. Reproduced with permission.^[174] Copyright 2022, Elsevier B.V.

amphiphilic copolymer, DSPE-SS-PEG-COOH. This nanoplatform demonstrated multiple functions including mitochondrial targeting, NIR-II fluorescence imaging, synchronous PTT, PDT, and immunotherapy (IMT). IR-FE-TPP was completely retained in NPs before reaching the tumor; after the accumulation of the copolymer in the tumor, the elevated GSH level in the TME cleaved the disulfide bond in the copolymer to release IR-FE-TPP, causing precise targeting of tumor mitochondria. Due to *in situ* amplification via mitochondrial targeting by both PTT and PDT, this functional nanoplateform exhibited adequate antitumor therapeutic and immunotherapeutic effects^[172] (Figure 6a,b). Yang et al. fabricated a novel amphiphilic copolymer with an active O (ROS)-responsive group in the main chain and TPP at the side chain end. PCN-224 serves as both a PS and carrier for the CO-releasing molecule CORM-401 that is loaded into its hollow structure (PCN-CORM); PCN-CORM was self-assembled and encapsulated in the mitochondria-targeting and ROS-responsive amphiphilic copolymer. HA, which provides a tumor-targeting function and protects the mitochondria-targeting group, was coated on the surface of the material, resulting in HA@MR@PCN-CORM NPs. Upon NIR light excitation, PCN-224 was activated to produce a large amount of ROS and triggered rapid intracellular release of CO. The released CO enhanced Fe death, amplified the PDT efficacy of PCN-224, and finally increased the antitumor efficacy of PCN-224 *in vitro* and *in vivo*^[173] (Figure 6c,d). Geng et al. proposed a block copolymer, poly(2-(N-oxide-N,N-dimethylamino)ethyl methacrylate)-block-poly(2-hydroxyethyl methacrylate) (OPDMA-HEMA), for the delivery of the anticancer agent celastrol. Amphiphilic polymer-celastrol conjugates self-assembled in aqueous solution. The OPDMA shell provided mitochondria-targeting ability to

celastrol. Compared to free celastrol, OPDMA-Cela exhibited appropriate water solubility and serum stability, low systemic toxicity, and higher anticancer efficacy^[174] (Figure 6e).

3. Nuclear-Targeting Strategies in Tumor Diagnosis and Treatment

3.1. Novel Biomarkers for Nuclear Targeting

Nucleus is the center that regulates the life activities of cells. It plays essential roles, for example, cytogenetic regulation, gene activation, and adjustments of cell metabolism and cell cycle. Increased frequency of chromosome segregation errors, also known as chromosomal instability (CIN), can alter gene expression and disrupt normal cell function. Thus, this process helps tumor cells acquire further malignant phenotypes including increased cell proliferation, metastasis, resistance to apoptosis, and genomic heterogeneity.^[175–178] A regular ellipsoidal shape of the nucleus is found in most normal cells. By contrast, those cancer cells often have irregular nuclear contours and altered sizes. However, in cancer cells, the nuclear contour is irregular, and the nuclear size is abnormal. Karyotype dynamics performs a central role in information-based genomics and genome-based macroevolution.^[179–180] Compared to whole genome sequencing, CIN detection is a cost-effective technique as it not only helps in screening patients who are at high risk for developing cancer, but also serve as an important tool in tumor diagnosis and management, providing valuable information that can help guide treatment decisions and improve patient outcomes.^[181–183] Many protein-related factors, for instance, genetic mutations and abnormal expressions of proteins that regulate cell division,

contribute to CIN in cancer cells.^[184–185] Typically, mutations in genes, such as *MYC*,^[186] *TP53*,^[187] *PTEN*,^[188] *MAD2*,^[189] *BRCA1*, and *BRCA2*,^[190] can increase the risk of chromosome segregation errors and promote cancer development. Taking AML as an example, TP53 mutations and deletions frequently occur in complex karyotype AML. In an AML cell with TP53 deficiency, spontaneous chromosomal abnormalities have been observed. Tolerance to structural chromosome aberrations is almost entirely restricted to TP53-knockout clones.^[191] Aberrant expressions of proteins, including Aurora kinase and centromere proteins, involved in mitosis can also disrupt chromosome segregation and promote tumor growth.^[192–193] Thus, these proteins are potential diagnostic markers for evaluating nuclear atypia and act as therapeutic targets in cancer treatment.^[194–196]

As an important subnuclear membrane-free organelle, the nucleolus plays a crucial role in the biogenesis of ribosomes, and ribosomes are the primary metabolic requirements of proliferating cells, particularly in invasive malignant tumors.^[197] Xue et al. have developed a γ -glutamyl transpeptidase (GGT) that can activate indole-quinolinium (QI)-based anthocyanins, which are composed of a new tripeptide fragment, QI-PG-Glu. QI-PG-Glu was utilized as a red fluorescent probe to rapidly detect GGT overexpression in A549 cells. Upon recognition by GGT, QI-PG-Glu underwent two-step activation to release HQI, which exhibited significant red fluorescence upon binding to rRNA, enabling imaging of nucleolus in living A549 cells. HQI also impeded rRNA biogenesis by reducing the transcription of RNA polymerase I, leading to apoptosis via the p53-dependent signaling pathway. Our findings suggest a promising approach for developing multifunctional, cancer cell-specific, nucleic-targeting fluorescent probes with potential anticancer effects.^[198] Moreover, multiple nuclear and nuclear-related biomarkers, such as AgNOR, Ki67, PCNA, and p53, have significant predictive importances in tumor diagnosis and recurrence.^[199–202]

3.2. Nuclear-Targeting Antitumor Agents or Drugs

Destruction of the DNA, chromosomes, and tubulin of cancer cells can very effectively inhibit the malignant behaviors of cancer cells.^[203–204] Inhibition of DNA synthesis using chemotherapeutic drugs or direct induction of DNA damage via radiation therapy has achieved considerable progress in cancer treatment.^[205] Chemotherapeutic drugs, for example, DOX, CDDP, oxaliplatin, and cyclophosphamide, can interfere with DNA repair mechanisms by entering the nucleus, leading to DNA damage and subsequently inducing cancer cell apoptosis.^[206–208] Pt drugs demonstrate both therapeutic and toxic effects on cells, which are attributed to the formation of covalent adducts not only between Pt complexes and DNA, but also between Pt complexes and RNA and various proteins. These processes play crucial roles in determining the molecular mechanisms underlying resistance and toxicity to Pt-based drugs. In the development of drug resistance, Upregulation of several transporters and increased repair of Pt-DNA adducts are the most significant processes.^[209] DNA damage-response enzyme inhibitors, such as ATR kinase, WRN helicase, and DNA polymerase/helicase Pol θ (Pol-Teta), are being explored as potential candidates to limit the impacts of these mechanisms of therapeutic resistance on cancer treatment.^[210]

Additionally, the combination of mitochondria-targeting drugs with DNA-toxic chemotherapeutic drugs can exert synergistic antitumor effects by inducing mitochondrial damage.^[211] For instance, the combination of metformin (which induces mitochondrial dysfunction) with the nitric oxide (NO) donor prodrug JS-K (which causes DNA damage) exhibits a synergistic antitumor effect on human renal cell carcinoma cells, which indicates that the high toxicities of combination drugs are related to the high level of intracellular ROS, changes in $\Delta\Psi_m$, and induction of DNA breakage.^[212]

3.3. Nuclear-Targeting Probes for Tumor Diagnosis

Abnormalities in nuclear and chromatin organization are indicators of many cancers. Designing stable and precise nuclear-targeting probes, specifically for live cell imaging to understand the dynamic functions of nuclei, can facilitate the diagnosis of cancers.^[213–215] Several nuclear-targeting probes have been developed for tumor diagnosis and treatment evaluation (Table 3). For example, optical coherence tomography (OCT) is an emerging optical technology that demonstrates considerable promise for early cancer diagnosis due to its rapid development.^[216,217] Nevertheless, conventional luminescent probe molecules used in cellular or subcellular imaging exhibit weak emissions upon dispersion or aggregation in aqueous media. To overcome this limitation, various aggregation-induced emission (AIE)-active luminogens (AIEgens) have been employed for imaging the cell nucleus, nucleon, and nucleic acids, demonstrating promising outcomes in the early diagnosis of cancer.^[218] Wu et al. designed a modular DNA-incorporated AIEgen probe (TPE-Py-DNA) for the detection and imaging of DNA adenine methylation (Dam) methyltransferase (MTase). The probe consists of two modules: a “turn-on” fluorescent AIEgen (TPE-Py) and a DNA sequence (Alk-DNA) that particularly recognizes the targeted strand. In an aqueous environment, TPE-Py-DNA remains almost non-fluorescent. Thus, the Dam MTase activities in the tumor tissues can be detected.^[219] Lei et al. developed a graphene-based tumor cell nuclear-targeting fluorescent nanoprobe (GTTN) for tumor targeting to overcome the low targeting rates of the methods based on EPR effects. GTTN is a graphene-like single-crystalline amphiphilic fluorescent probe functionalized with sulfonic and hydroxyl groups. This probe can cross the CM and specifically target the tumor cell nucleus via the CM permeability targeting (CMPT) mechanism (Figure 7a). With a good ability to distinguish tumor tissue at an early stage, GTTN can track the metastasis of tumor cells (Figure 7b,c), offering an effective and accurate tumor cell targeting strategy for tumor diagnosis and treatment.^[220] Telomerase reactivation is a common characteristic of cancer cells that enables replicative immortality.^[221–222] To provide a potential basis for the early diagnosis and management of cancer, Gang et al. have designed a nanoprobe based on QDs and FRET that can dynamically monitor changes in telomerase activity in tumor cells during drug treatment.^[223] Groysbeck et al. produced Au NPs whose surfaces were functionalized with SV40 nuclear localization signal (NLS)-containing peptides and 2 kDa PEGs (Figure 7d). The NPs were coordinated with thioaminobenzoate and thionitrobenzoate and demonstrated quick nuclear import owing to the incorporation of NLS into the PEG coverage.^[224]

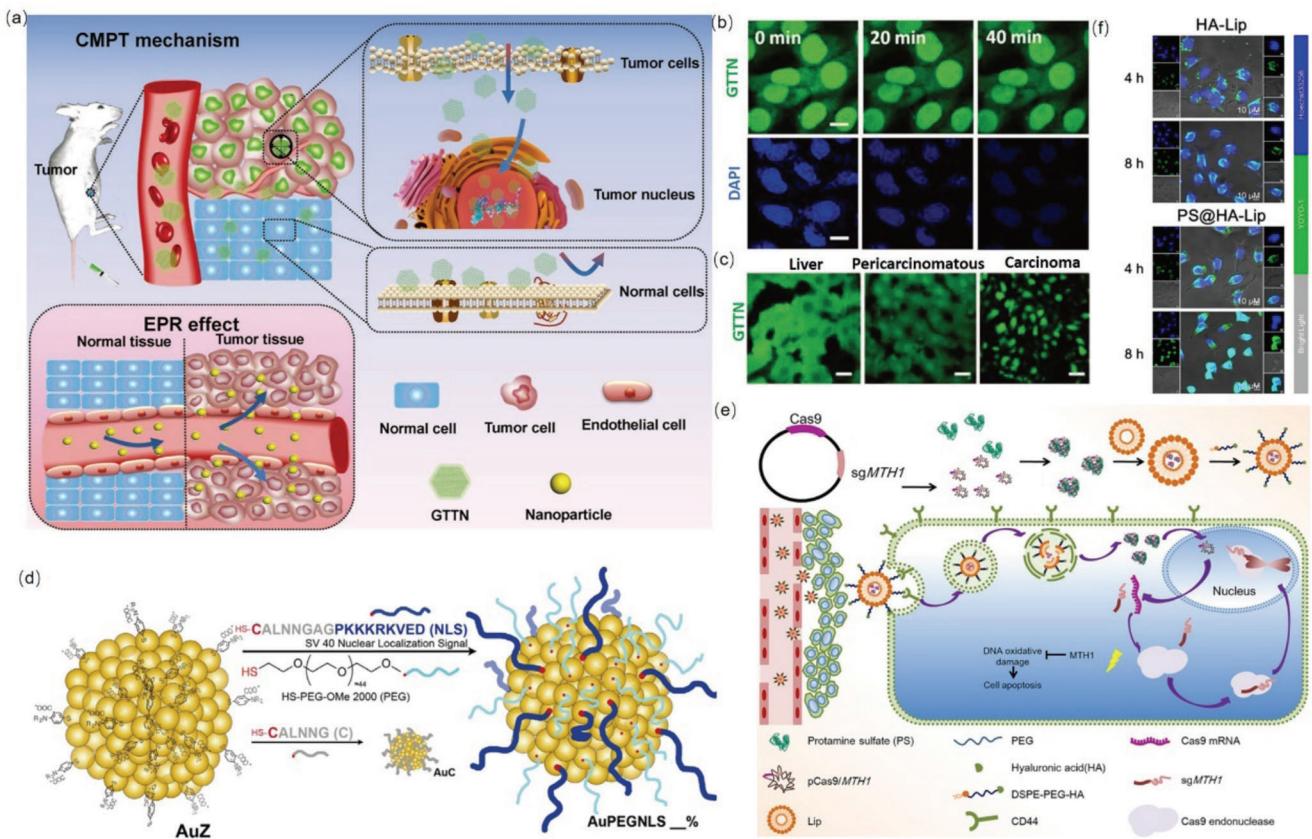


Figure 7. a) GTTN can recognize tumor cells by changing the permeabilities of tumor cells and target tumor nuclei by the CMPT mechanism. b) GTTN and DAPI were continuously irradiated for 40 min. c) Confocal images of GTTN fluorescence signals in liver/pericarcinomatous/tumor tissue frozen sections of orthotopic tumors. a-c) Adapted with permission. Reproduced with permission.^[220] Copyright 2019, Wiley-VCH. d) Schematic of polyethylene glycol and nuclear localization signals of peptide-decorated AuNPs. Reproduced under the terms of Creative Commons Attribution CC BY License.^[224] Copyright 2023, The Authors, published by Wiley-VCH GmbH. e) Schematic of the effective nuclear-targeted delivery of pMTH1 by PS@HA-Lip in NSCLC treatment. f) Intracellular distribution of YOYO-1-labeled HA-Lip/pMTH1 and PS@HA-Lip/pMTH1 in A549 cells after incubation for 4 and 8 h. Reproduced with permission.^[230] Copyright 2022, Acta Materialia Inc.

3.4. Nuclear-Targeting Functional Materials for Tumor Treatment

Cell nucleus-targeting nanotherapies, such as chemotherapy, gene therapy, PDT, and PTT, have demonstrated promising anti-tumor properties.^[225] Several barriers, including the CM, cytosolic trafficking, and nuclear envelope, prevent the nuclear delivery of antitumor agents.^[226] The nuclear envelope is composed of two nuclear membranes (inner and outer membranes), nuclear pore complexes (NPCs), and an underlying nuclear lamina. It acts as a barrier that separates the nuclear contents from the cytoplasm and restricts the free passage of molecules.^[227] Hence, carefully designed NPs are required to enable nuclear targeting and effective nuclear delivery. As an example, Pogorzelska et al. have constructed a liposomal formulation that contains DOX and sulforaphane, a nutraceutical. This formulation can deliver both compounds to cancer cells and can directly deliver DOX to the cell nucleus. DOX achieved higher accumulation in the cell nucleus with the help of sulforaphane. In contrast, the ROS status of the cell is slightly affected. Additionally, the formulation exhibits lower cytotoxicities in normal cells and in a 4T1 mouse model of TNBC.^[228]

3.4.1. Nuclear-Targeting Liposomes/Lipid NPs in Cancer Treatment

Liposomes have been considered promising and versatile drug/gene vesicles, while endosomal escape, perlysosomal degradation, and nuclear uptake have largely limited their actual applications.^[229] Wang et al. developed a liposome-coated protein/DNA complex, PS@Lip/pCas9, for the targeted delivery of CRISPR/Cas9 plasmids to the nuclei of tumor cells (Figure 7e,f). Protamine sulfate (PS) was employed to condense the plasmids and facilitate nucleus-targeted delivery. The liposome coating protected the complex from nuclease degradation. The complex was modified with distearoyl phosphoethanolamine-PEG-HA to actively target tumor cells. PS@Lip/pCas9 inhibited the growth and metastasis of NSCLC and enhanced cell apoptosis by inducing genome editing effects.^[230] Darabi et al. prepared SLN/DOX/Dexa/CD44/EGFR aptamers based on DOX-containing solid lipid NPs (SLNs). To enhance the nuclear delivery of DOX, they synthesized 6-lauroxyhexyl BOC-ornithine (LHON) and chemically attached it to dexamethasone (Dexa) to form Dexa-LHON complexes. The SLN/DOX/Dexa/CD44/EGFR aptamers demonstrated potent antiproliferative activities.^[231] Integrin $\beta 3$ ($\alpha v \beta 3$ and $\alpha IIb \beta 3$) is an important cell adhesion

molecular family that is overexpressed in both the CMs and perinuclear regions of cancer cells.^[232–233] Zhang et al. have identified a specific ligand, B3int, consisting of arginine–tryptophan–(D-arginine)–asparagine–arginine, which selectively targets integrin $\beta 3$ -overexpressing cancer cells. B3int-modified liposomes (B3int-LS-DOX) can selectively deliver DOX to the nuclei of prostate cancer cells by targeting integrin $\beta 3$, thereby significantly improving the anticancer effects of DOX.^[234]

3.4.2. Nuclear-Targeting Metal NPs

Inorganic NPs (INPs) composed of metal and metal oxides exhibit large specific surface areas and high activities; therefore, they are ideal candidates for functionalization with various coatings, specific agents, and drug molecules for antitumor and antiviral therapies.^[235] Unique features of magnetic NPs (MNPs)^[236–237] and Au NPs^[224] have been discovered, and these NPs have been utilized for constructing functional materials that target cancer cell nuclei. Proton relaxation in specific tissues is enhanced by MNPs of iron oxides and ferrites. Thus, more ideal MRI contrast agents of MNPs are developed, which could also be used for hyperthermia therapy, controlled drug release, MRI, and biosensing therapy.^[238] For example, Peng et al. designed an efficient nuclear-targeting monodisperse MNP using transferrin and TAT peptide for conjugation. TAT peptides can effectively target the nucleus. MNPs demonstrate high photothermal conversion efficiencies ($\approx 37\%$) and considerable photothermal stabilities and can be employed for imaging guidance and PTT.^[239] Özçelik and Pratz have developed 40 nm Au NPs with abilities to target the nuclei of cancer cells using arginine-glycine-asparagine (RGD) and NLS peptides. The RGD peptides guide the material to target cancer cells, and the NLS peptides are used for targeting the nucleus. Therefore, cell death is activated by X-ray irradiation. Peptide-modified Au NPs enhance radiosensitization by targeting the nucleus.^[240] In addition to MNPs and Au NPs, other metal NPs have been fabricated for cancer imaging and therapy; for instance, Xie et al. designed intelligent biodegradable hollow manganese dioxide (HMnO_2) NPs (HMnO_2 -MSC-TAT NPs) to efficiently achieve chemoimmunotherapy for cancer treatment; HMnO_2 -MSC-TAT NPs comprised a human umbilical cord mesenchymal stem cell (hUC-MSC) membrane coating for tumorotropic accumulation and a TAT peptide-modified membrane structure for nuclear targeting; these NPs exhibited significant tumor-inhibiting functions and potentials for cancer immunotherapy^[241] (Figure 8a).

3.4.3. Nuclear-Targeting Dendrimer Nanoplatforms

Generations 5 and 6 (G5 and G6) PAMAM dendrimers are highly efficient nonviral carriers for gene and drug delivery.^[242–243] Lu et al. synthesized RGdyC-mPEG-PAMAM, a nuclear-targeting drug carrier composed of Arg-Gly-Asp (RGdyC) and $\alpha v \beta 3$ integrin-targeting ligand conjugated to a PEGylated fifth generation PAMAM dendrimer (mPEG-PAMAM); RGdyC-mPEG-PAMAM regulated the release of arsenic trioxide at different pH levels and exhibited lower cytotoxicity on human brain microvascular endothelial cells. RGdyC-mPEG-PAMAM induced cell

apoptosis and cell cycle arrest in C6 cells, which demonstrated high uptake of the drug carrier.^[244] A bifunctional RGDTAT (RT) peptide-modified PEG-PAMAM dendrimer conjugate, RGDTAT-PEG-PAMAM (RTPP), was developed for cancer therapy. The peptide containing the RGD motif, conjugated with the cell-penetrating peptide TAT, yielded a bifunctional peptide, RT. Finally, this functional material showed high cell selectivity and enhanced cellular uptake in $\alpha v \beta 3$ -overexpressing cells.^[245] Zhao et al. prepared a novel polymer-dendrimer hybrid NP-based nanosystem for efficient and controlled codelivery of DOX and paclitaxel (PTX) to cancer cells. The nanosystem demonstrated rapid and effective uptake by the cancer cells, and the delivered drugs were sustainably and efficiently released within the cells, synergistically inducing considerable changes in both the nucleus and tubulin patterns.^[246]

3.4.4. Nuclear-Targeting CNTs

The exceptional properties, including small sizes and high specific surface areas, of CNTs enable their adsorption on biological substrates, facilitating their numerous applications, for example, as drug delivery carriers, cancer imaging agents, and cancer treatment modalities.^[247–250] For instance, Lu et al. functionalized MWCNTs with PAA to load DOX, and then, the resulting MWCNTs were decorated with iron oxide MNPs (IONPs) to develop a magnetic dual-targeted nanocarrier. DOX exhibited high cytotoxicity toward U87 human glioblastoma cells and was intracellularly released and transported to the nucleus, whereas the nanocarrier remained in the cytoplasm.^[251]

3.4.5. Nuclear-Targeting SNs

SNs have been used for imaging, transport, drug delivery, and radiosensitization.^[252] For example, MSNs were thermally etched with dilute sulfuric acid to create a framework, into which HA, CaO_2 , p53, and DOX were loaded to form NP complexes, $\text{SiO}_2 @ \text{CaO}_2 @ \text{DOX} @ \text{P53-HA}$. The material was taken up by lung cancer cells, with gradual enrichment of DOX and Ca^{2+} within the cells. Both in vitro and in vivo experiments verified the antitumor effects of $\text{SiO}_2 @ \text{CaO}_2 @ \text{DOX} @ \text{P53-HA}$.^[253] Recently, accumulating studies have developed nuclear-targeting SNs for the delivery of small-molecule drugs. For instance, surface-modified biodegradable silica nanocapsules (BSNPs) were conjugated with three different NLS peptides (TAT, PV24, and NMTAS) to improve their cell-penetrating and nuclear-localizing properties. Surface-modified BSNPs encapsulating proteins (EGFP: 27 kDa; DNase I: 32 kDa; and mAbH3: 150 kDa) were fabricated to improve the capability of endosomal escape and nuclear-targeted delivery of proteins upon conjugation with DNA-carrying NPs^[254] (Figure 8a–g). Ma et al. developed a nanosystem (MSNs/DOX/DNA) with the guidance of CRISPR-dCas9 for targeting telomerase. Thus, ideal nuclear-targeting functions and controlled release of anticancer drugs were both achieved.^[255]

3.4.6. Nuclear-Targeting CQDs

Numerous biomolecules and biopolymers, such as proteins, amino acids, nucleic acids, carbohydrates, and vitamins, have

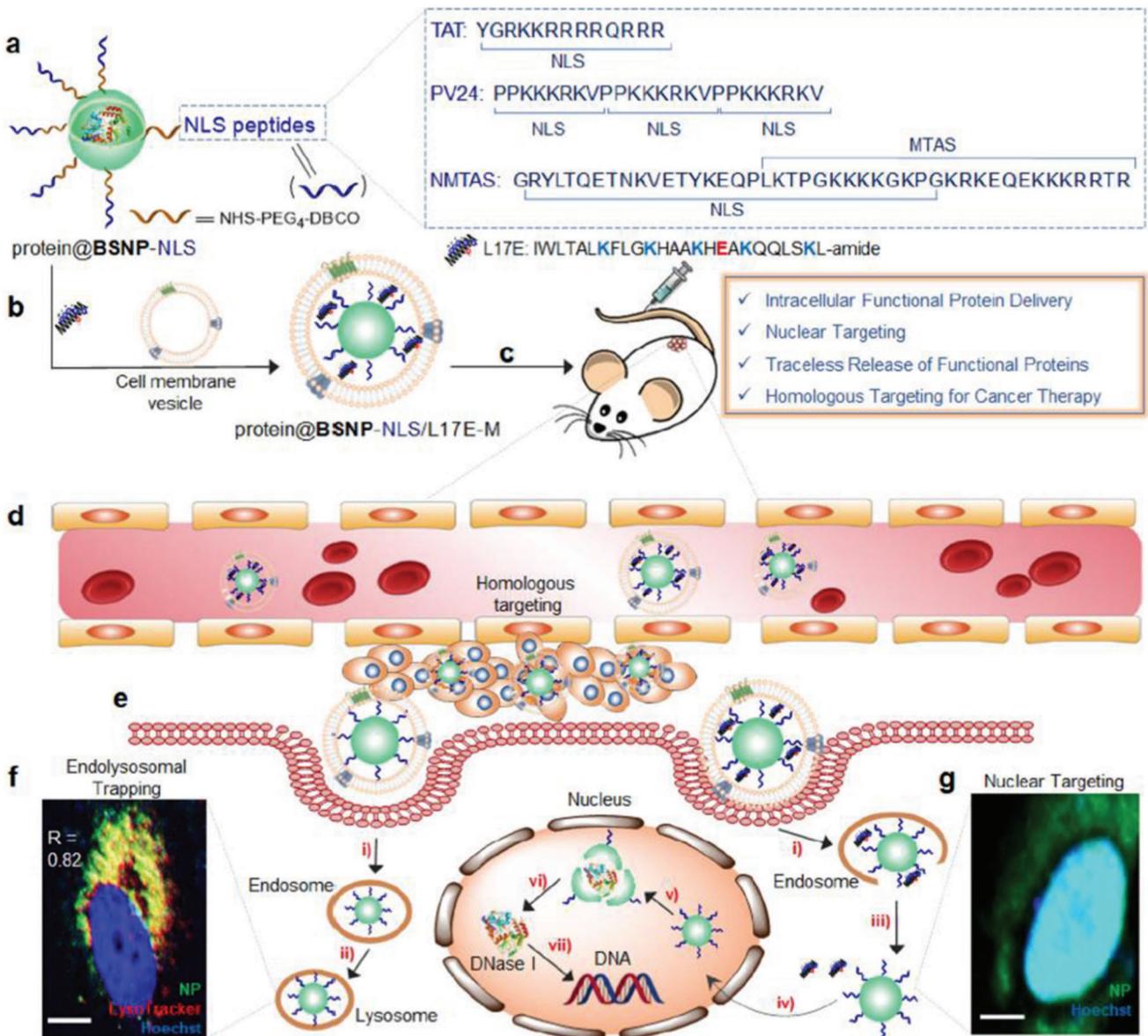


Figure 8. a–g) Schematics showing nuclear-targeted delivery of native functional protein/antibody using protein@BSNP-NLS/L17E-M. Reproduced with permission.^[254] Copyright 2023, Elsevier Ltd.

been used for the fabrication of CQDs.^[256–257] A cross-linking system comprising TiO₂-immobilized Dopa-decyl CD (D-CD) and zwitterionic-formed CD (Z-CD) was formed by boronate ester linkages for nuclear targeting. The (C-CD/TiO₂) group demonstrated fluorescence “off” at physiological pH and upregulated the proapoptotic markers P53 and BAX in the tumor. When combined with PDT, this material exhibited enhanced antitumor effects, since it has excellent biocompatibility, high sensitivity, and selective imaging abilities as a theragnostic sensor^[258] (Figure 9a,b). Similar to other CQDs, graphene QDs (GQDs) can be used to carry proteins, genetic materials, or drugs, suggesting that they are promising candidates for tumor diagnosis and tumor-targeting therapy.^[259–260] GQDs were synthesized and conjugated with the EGFR-antagonist peptide GE11 followed

by loading of the clinical chemotherapeutics CDDP and DOX to form the GQDs@GE11/CDDP/DOX nanoprobe (Figure 9c). This functional material targets nasopharyngeal carcinoma with positive expression of EGFR in the nucleus, significantly restraining tumor cell proliferation and growth both *in vitro* and *in vivo*.^[261] Cationic CDs (CCDs) are potential NPs that can penetrate nuclear membranes. Chen et al. developed Y15-conjoined CCDs (Y15-CDs) using Y15, folic acid, and 1,2-ethylenediamine as precursors via a hydrothermal approach. Y15-CDs target the nucleus and demonstrate anticancer abilities by binding to DNA via electrostatic interactions and partially intercalative binding modes. Notably, Y15-CDs exhibit more inhibition abilities toward cancer cells than toward normal cells, implying that they can selectively prevent the growth of cancer cells (Figure 9d,e).^[262]

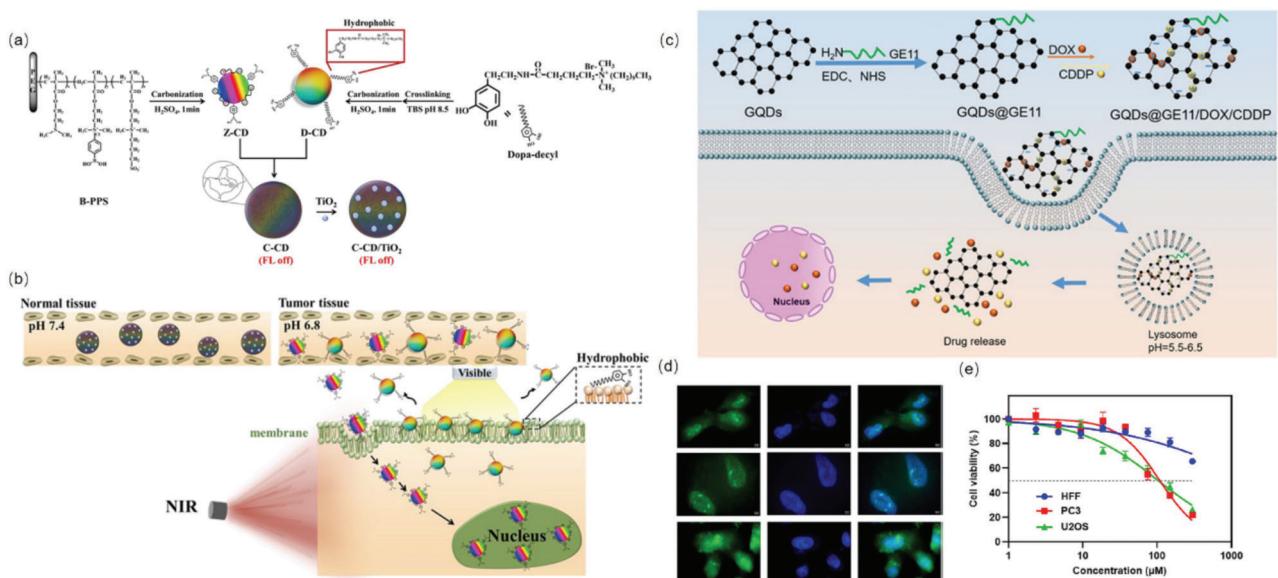


Figure 9. a) Schematic illustrating the design of pH-responsive C-CD/TiO₂ for nuclear targeting. b) Schematic of the application of pH-responsive C-CD/TiO₂ for nuclear-targeted bioimaging under visible-light irradiation with photothermal therapy. Reproduced with permission.^[258] Copyright 2020, American Chemical Society. c) Schematic of the transport of DOX and CDDP to cells by the GQD@GE11/DOX/CDDP complex in tumor therapy. Reproduced under the terms of the Creative Commons CC BY License.^[261] Copyright 2021, The Authors, published by Wiley Periodicals LLC. d) Fluorescence images of human foreskin fibroblast (HFF), osteosarcoma (U2OS), and prostate cancer (PC3) cells incubated with Y15-CDs (1 mg mL^{-1}). e) Effects of Y15-CDs on the viabilities of HFF, PC3, and U2OS cells. Reproduced with permission.^[262] Copyright 2023, Elsevier Inc.

4. ER-Targeting Strategies in Tumor Diagnosis and Treatment

ER has wide functions in mediating protein synthesis, folding, modification, transport, and lipid metabolism in eukaryotic cells. Accumulation of misfolded or unfolded protein triggers the unfolded protein response (UPR), causes ER stress or even initiate cell apoptosis.^[263–264] Disruption of ER function can lead to several diseases including cancer. In cancer cells, the ER may be overwhelmed by the accumulation of proteins and lipids, causing ER stress and activation of the UPR pathway. Although the initial activation of the UPR can help cells survive by reducing protein synthesis and inducing cell repair mechanisms, persistent UPR activation can promote cancer development.^[265] ATF6, IRE1 α , and PERK are three ER-anchored transmembrane receptors that coordinate to restore ER homeostasis and promote cell survival when ER stress is induced. They also mediate tumorigenesis, tumor growth, metastasis, and chemotherapy resistance.^[266–267] Additionally, cancer cells stimulate mitochondrial metabolism by releasing mitochondrial metabolites, enzymes, and ions from the ER, providing a platform for tumorigenesis.^[268–269] Other studies have revealed that ER stress can also promote tumor invasion and metastasis by activating signaling pathways, such as IL-6-JAK-STAT3, via glutathione peroxidase 8 (GPx8) and UPR.^[270] Abnormal expression of the ER-resident protein Sec62 indicated inferior prognosis in CRC patients. Sec62 enhances the expression of UCA1 and stimulates the malignant transformation of CRC cells by triggering the MAPK/JNK signaling pathway.^[271] B-cell receptor-associated protein 31 (BCAP31), a protein located in the ER, is highly expressed in various cancers. It influences CRC cell proliferation via the Emerin/ β -catenin axis.^[272] Linoleic acid (LA) enhances the formation of ER-mitochondria contacts and

promotes Ca²⁺ signaling, mitochondrial energetics, and CD8⁺ T-cell (CTL) activity, ultimately exerting an enhancing effect on antitumor immunity.^[273] These findings suggest that ER is involved in tumor progression, and detection of ER has significant clinical implications for cancer diagnosis and treatment.

4.1. ER Probes in Cancer Diagnosis

Numerous ER-specific antibodies, including BCAP31, calnexin, glucose-regulated protein 78 (GRP78), Ero1 α , and protein disulfide isomerase, have been extensively utilized for ER labeling and cancer diagnosis.^[274–275] Fluorescent probes exhibit advantages such as high sensitivities, high selectivities, appropriate spatiotemporal resolutions, and live-cell imaging capabilities. ER-targeting fluorescent probes have been developed for tumor diagnosis.^[276] ERAP1 is a major aminopeptidase that trims N-terminal residues of antigenic peptides and serves as an editor of the peptide repertoire. It is altered in tumor tissues as compared to that in normal tissues.^[277] Chemical inhibition of ERAP1 is a viable approach to manipulate the immunopeptidome of cancer.^[278] SNCL is a two-photon (TP) fluorescent probe fabricated by Xu et al. It consists of a TP fluorophore (1,8-naphthalimide), a trigger moiety (l-leucine), and an ER-targeting group (methyl sulfonamide moiety). SNCL is highly sensitive to ERAP1 and can be used to image ERAP1 activities in living cells. The content of ERAP1 is dependent on the redox state of the ER. SNCL monitors ERAP1 in tumor tissue with an imaging depth of 50–120 μm .^[279] GRP78 is the master regulator of the UPR in the ER and can regulate ER stress and improve tumor cell viability under hypoxia, low glucose, and other stress conditions.^[280] Zhao et al. have constructed the GRP78-targeted molecular probe

Ga-68-radiolabeled DOTA-VAP conjugate ($[^{68}\text{Ga}]\text{DOTA-VAP}$) based on VAP peptide.^[281] The probe has good stability and is available for imaging in positron emission tomography (PET). Advantages, such as a more advanced ability to distinguish tumor cells and normal cells, were identified on the probe when compared with the most widely used molecular PET imaging agent 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F -FDG).^[282] Therefore, this designed probe affords a noninvasive method for accurate molecular typing of TNBC.^[281]

Hypoxia is closely related to various diseases including solid malignant tumors. Identifying hypoxic tissue is reasonable in therapy planning.^[283] ER-targeting probes can directly reflect cell functions under stimuli and facilitate the diagnosis of cancers.^[284–285] Using these probes, live-cell detection of several substances, including hydroxyl radical ($\cdot\text{OH}$),^[286] esterase,^[287] biothiols (cysteine, homocysteine, and GSH),^[288–289] hydrogen sulfide (H_2S),^[290] CYP2J2,^[291] mobile Zn^{2+} ,^[292] methylglyoxal,^[293] 1,4-dithiothreitol,^[294] carboxylesterase 2,^[295] formaldehyde (FA),^[296] and Ca^{2+} ^[297] inside or outside the ER can be achieved. For example, the H_2S level is usually abnormally upregulated under hypoxic conditions and may act as a biomarker of the hypoxic microenvironments of tumors.^[298] Kafuti et al. developed the fluorescent probe ER-Nap-NBD for assessing H_2S levels in solution and living systems. This probe mainly consists of three parts: a naphthalimide fluorophore that functions as a signal reporter, 7-nitro-1,2,3-benzoxadiazole amine that serves as the responsive moiety, and a sulfonamide part that is used for ER targeting. This probe successfully visualized exogenous/endogenous H_2S in tumor cells and zebrafish.^[299] Ca^{2+} signals are crucial molecular devices for sensing and integrating signals from the TME and function as a potential target in tumor treatment.^[300] As the primary intracellular Ca^{2+} store, the ER plays an essential role in maintaining Ca^{2+} homeostasis by coordinating with other organelles and the plasma membrane.^[301] Notably, during the uncontrolled proliferation of cancer cells, the connection between mitochondria and ER emerges via “mitochondria-associated ER membranes” (MAMs). Ca^{2+} transfer occurs in MAMs, and mitochondrial biology is altered, causing malignant progression of cancer.^[302–303] Recently, an ER-targeting genetic probe, namely, ER-GCaMP6f,^[297] has been designed that can identify Ca^{2+} signaling dynamics within the ER. In the future, this probe is expected to be utilized for measuring tumor Ca^{2+} within the ER.

4.2. ER-Targeting Functional Materials for Tumor Treatment

Targeting of altered ER functions, such as ER stress^[304] and MAM dysregulation,^[305] has been applied in cancer treatment. For instance, bortezomib, the first ER stress-targeting therapeutic drug to be used in clinical practice, can inhibit proteasome in multiple cancers.^[306–309] Ursodeoxycholic acid demonstrated a synergistic effect with bortezomib in glioblastoma multiforme via protracted ER stress.^[310] implying that bortezomib-mediated antitumor effects can be boosted by combining bortezomib with other ER stress mediators. Other strategies for targeting ER stress in cancers include targeting ER stress sensors (for example, IRE1, PERK, and ATF6)^[311] and ER-associated protein degradation (ERAD).^[312–313] For instance, $1,25(\text{OH})_2\text{-D}_3$, an

active metabolite of vitamin D, downregulated the expressions of ERAD components and the IRE1 α and PERK branches of the UPR in LNCaP human prostate cancer cells, thus suppressing tumor progression.^[314] However, MAM-resident proteins are also therapeutic targets in cancers. For example, FUN14 domain-containing 1 (FUNDC1) is a crucial MAM and mediates mitochondrial division and mitophagy. FUNDC1 overexpression is associated with inferior outcomes in BC patients.^[315] Functionally, FUNDC1 upregulation promotes Ca^{2+} cytosolic influx from the ER and extracellular environment, drives the malignant behaviors of BC cells, and enhances angiogenesis and neoangiogenesis by inducing MAM formation.^[315–316] These studies suggest that targeting FUNDC1-dependent MAMs may be a promising approach for treating cancer and diseases with defective angiogenesis. As another vital protein in MAM production, 75-kDa glucose-regulated protein (GRP75) induces CDDP resistance in ovarian cancer by mediating ER-to-mitochondria Ca^{2+} transfer.^[317] Interestingly, self-assembled GRP78-targeting small interfering RNA (siRNA) nanostructures exhibit potent and long-lasting anticancer activities.^[318]

Recently, many functional nanomaterials (for example, NPs, niosomes, liposomes, and intravenous hydrogels) have been designed and applied in anticancer therapies by mediating ER dysfunction.^[319] For instance, mesoporous calcium carbonate NPs were loaded with curcumin (CUR) and then coated with a platelet (PLT) membrane. The designed functional material, termed PLT@MCC/CUR, facilitated Ca^{2+} release from the ER, inhibited Ca^{2+} efflux, disrupted mitochondrial Ca^{2+} homeostasis, and finally promoted mitochondrial apoptosis signaling pathway activation only in tumor cells (Figure 10a,b).^[320] CT@CM NPs are a redox-responsive nanomedicine formulation developed by Guo et al. They are polymeric NPs loaded with P dendrimer-Cu (II) complexes (1G3-Cu) and Toy and coated with cancer CMs. These NPs with sizes of 210 nm are stable under physiological conditions; nevertheless, they rapidly dissociate in the reductive TME. 1G3-Cu aggravates mitochondrial dysfunction, whereas Toy enhances ER stress, leading to significant tumor cell apoptosis and immunogenic cell death. Moreover, GCT@CM NPs can effectively prevent tumor recurrence and metastasis, thus potentiating tumor IMT.^[154] Pep42 cyclic peptide selectively targets GRP78 on the cancer CM, specifically in the ER.^[321–322] Hasani et al. constructed Pep42-targeted IONPs functionalized with β -cyclodextrin (β CD) containing DOX, named $\text{Fe}_3\text{O}_4\text{-}\beta\text{CD-Pep42-DOX}$ (Figure 10c). TEM images show that the nanoplatforms had spherical morphologies and core-shell structures with sizes of \approx 17 nm. Functionally, $\text{Fe}_3\text{O}_4\text{-}\beta\text{CD-Pep42-DOX}$ exhibited considerable in vitro and in vivo anticancer abilities.^[323] Wan et al. designed a nanoplatform that was based on hollow mesoporous $\text{Cu}_{2-\text{x}}\text{-XS}$ ($\text{HMCu}_{2-\text{x}}\text{-XS}$) for targeting ER, which was realized by modifying $\text{HMCu}_{2-\text{x}}\text{-XS}$ with *p*-toluenesulfonamide. The vascular inhibitor celecoxib (CXB) was loaded into the NPs. ER-HMCu_{2-x}S/CXB can restrain the recurrence and metastasis of TNBC by combining photoablation and microenvironment remodeling.^[323] Other nanomaterials, such as the Cy7.5-TG@GPM nanoplatform^[324] and tLyP-1/PR-619/ Fe_3O_4 @PCM (tPF@PCM),^[325] also demonstrated prominent antitumor effects. These ER-targeted nanomaterials provide imaginative methods for treating conventional therapy-resistant cancers by targeting ER.

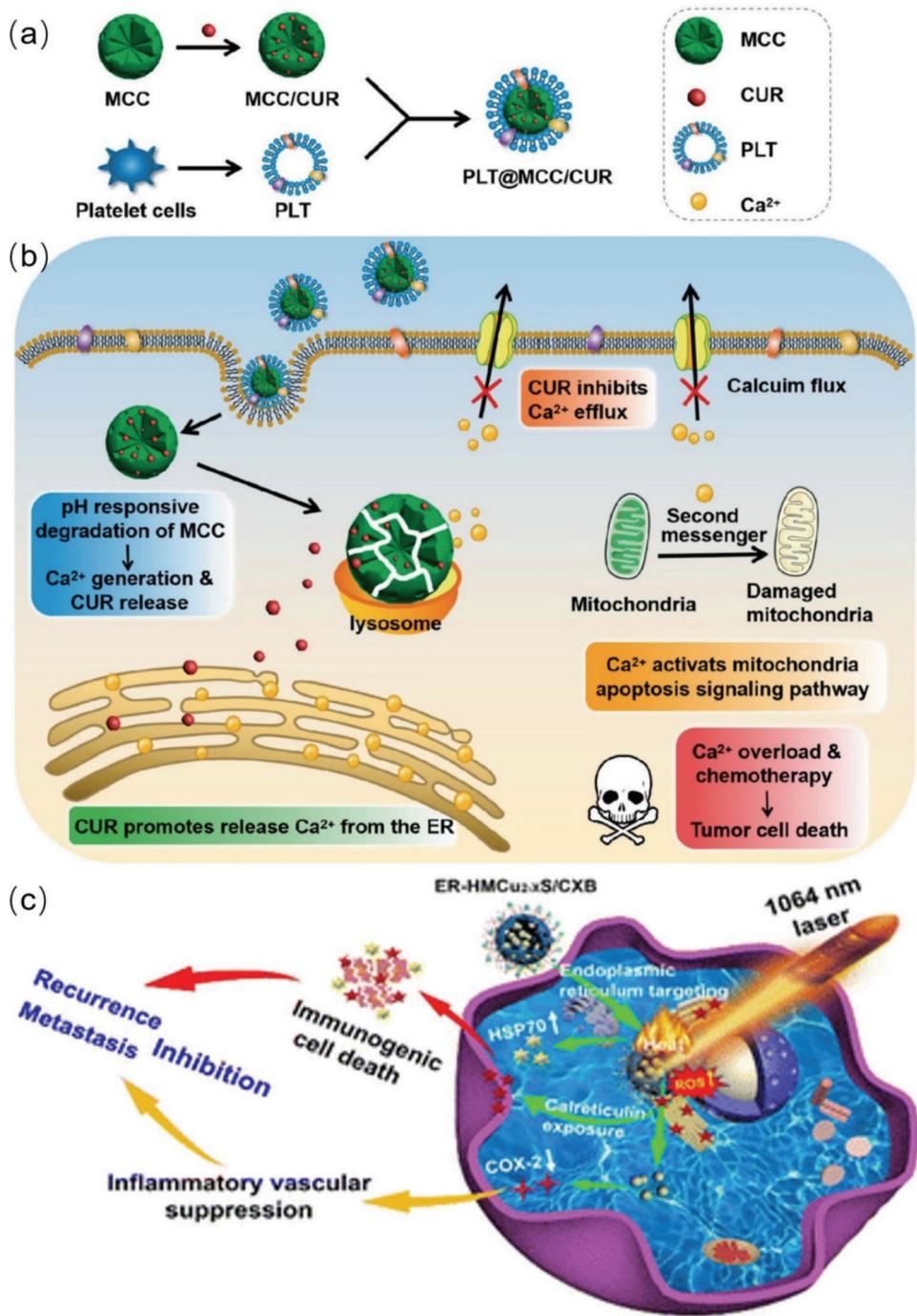


Figure 10. a) Schematic of the design of PLT@MCC/CUR. b) Schematic of the mechanism of the biomimetic Ca²⁺ nanogenerator-mediated synergistic combination of Ca²⁺ overload therapy and chemotherapy based on an ion interference strategy. Reproduced with permission.^[320] Copyright 2021, Taylor & Francis. c) Schematic illustrating the consecutive steps for the formation of endoplasmic reticulum-targeting multifunctional Fe₃O₄-βCD-Pep42 nanoplateforms. Reproduced with permission.^[323] Copyright 2023, American Chemical Society.

5. Lysosome-Targeting Strategies Based on Functional Materials for Tumor Diagnosis and Treatment

Lysosomes are membrane-bound organelles containing hydrolytic enzymes.^[326] Notably, lysosomes play crucial roles in

both cancer initiation and progression. Lysosomal enzymes affect the invasive abilities of cancer cells as they degrade the extracellular matrix and allow cancer cells to migrate and invade surrounding tissues. Additionally, lysosomes can help cancer cells survive under stressful conditions, including nutrient deprivation and hypoxia, by providing energy and nutrients to these cells

via autophagy.^[327–329] Overall, lysosomes perform important roles in cancer development and treatment.

5.1. Lysosome-Targeting Probes for Cancer Diagnosis

Lysosome-targeting probes can be used in numerous applications such as lysosome imaging in live cells, measurement of lysosomal activity, and drug discovery. Lysotracker Red is an extensively used fluorescent probe that is capable of detecting and labeling lysosomes in live cells.^[330] Although Lysotracker dyes do not particularly label lysosomes or autophagosomes within the cell, they are cost-effective and easier to use than live-cell LCB-GFP-tagged experiments and can be employed to analyze patient cells.^[331] Furthermore, the fluorescence intensity of Lysotracker may indicate alterations in lysosomal pH due to the accumulation of Lysotracker in acidic organelles.^[332] BODIPY derivatives have become a cornerstone for innovative fluorescent lysosome-labeling strategies.^[333] BODIPY derivatives are characterized by appropriate photophysical properties, outstanding photostabilities under biological conditions, and facile synthesis, which expands their application areas.^[334] Fluorescent lysosome-targeting probes based on BODIPY fluorophores comprising morpholine and nitro groups enable imaging of lysosomes in hypoxic cells.^[335] Moreover, fluorescent probes designed by conjugating three different BODIPY donors to rhodamine and merocyanine acceptors can be used for ratiometric determination of lysosomal pH variations.^[336] More fluorescent probes based on BODIPY derivatives have been designed for assessing lysosomal H₂S,^[337] NO,^[338] H₂O₂,^[339] viscosity,^[340] cholesterol,^[341] and Fe²⁺ and H⁺.^[342] In addition to BODIPY derivatives, other fluorophores including donor-acceptor-donor (D-A-D)-type fluorophores^[343] and heterocyclic sterol probes^[344] can be utilized for designing lysosomal probes. Wang et al. created a new chemotype probe, 4,7-bis(4-(2-morpholinoethoxy)phenyl)benzo[c]-[1,2,5]thiadiazole-5,6-diamine (MBTD), by incorporating an o-phenylenediamino (OPD) moiety into a D-A-D-type fluorophore based on a dual intramolecular charge transfer (ICT) mechanism. MBTD demonstrates a large stroke shift, high NO specificity, and high acid tolerance, which facilitate an acid-promoted response to NO and improves the spatial resolution to lysosomal NO by excluding background noise from nonacidic organelles.^[345]

Recently, lysosomal probes have been prepared for tumor diagnosis (Table 3). HcyCl-F is a TP turn-on fluorescent reporter designed by Fan et al. for visualizing lysosomal α-L-fucosidase (AFU) and early diagnosis of liver cancer. The designed probe HcyCl-F quickly and accurately responds to AFU in lysosomes, exhibiting a strong fluorescence signal in the tumor tissue of liver cancer-bearing mice. Additionally, HcyCl-F is capable of detecting liver tumors in stage I.^[346] Zong et al. have developed a dual-locking nanoprobe using NIR hemicyanine CyNH₂ that has two orthogonal stimuli: cancer cell lysosomal pH (first “lock”) and lysosome-overexpressed cathepsin B (CTB, second “lock”), which trigger NIR fluorescence turn-on and drug activation, thereby improving the specificity of cancer imaging and therapy^[347] (Figure 11a). Similarly, an enzyme-activated ratiometric TP fluorescent probe (RN-GLU) for detecting lysosomal β-glucuronidase (GLU),^[348] two naphthalimide-based fluorescent

probes for sensing FA in cells and lysosomes,^[349] and the fluorescent probe Lyso-Gal for evaluating lysosomal β-galactosidase^[350] have been constructed. Jia et al. developed a fluorescent probe (MACaP9) based on dysregulated energy metabolism of cancer cells. MACaP9 specifically responds organelles with lower pH values. In addition, MACaP9 shows distinct fluorescence signals based on pH variations in tumors and normal tissues. Thus, MACaP9 is an effective probe for detecting tumor extracellular pH.^[351]

Analysis of lysosome dynamics helps tumor diagnosis.^[352–354] Yu et al. synthesized a lysosome-targetable fluorescent probe, NIM-3, which demonstrated features including high selectivity, high photostability, and low cytotoxicity. Lysosomal positioning studies based on the fluorescent probe revealed a new and potential anticancer therapy: the combination treatment of TNFα and chloroquine (a lysosomal pH elevator).^[355] Zhou et al. have designed an NIR-light-triggered ICG-based PCL core/P(MEO₂MA-b-HMAM) shell nanocomposite (PPH@ICG) that can internalize into the lysosomal compartments under NIR, suggesting that this functional material has well potentials in lysosome imaging (Figure 11b).^[356] Overall, lysosome-targeting probes are important tools for examining lysosome function and localization and can have crucial implications for understanding lysosome-related processes in cancers and developing new antitumor therapies.

5.2. Lysosome-Targeting Functional Materials for Cancer Therapy

Targeting lysosomes, which are involved in cancer development and chemoresistance, can be a promising therapeutic strategy for overcoming chemoresistance in cancer cells.^[357–358] Gao et al. created a multifunctional nanomaterial, FBD-M, composed of a BODIPY fluorophore, a pentafluorobenzene group for carrying O, a morpholine group for lysosome targeting, and an aromatic N mustard group for chemotherapy, which conferred sensitivity to FBD-M for NIR phototherapy (Figure 11c). FBD-M exhibited multiple characteristics such as ideal NIR emission and absorbance, activity of photosensitivity, high stability under photothermal stimulation, accurate targeting on lysosome, less toxicity, and high efficiency against hypoxic tumors, indicating that FBD-M can function as an ideal multifunctional theragnostic agent.^[359] He et al. developed functional NPs, PTX-PMP/WPH-NPs, comprising two functional polymers: PMP containing an MMP-2 enzyme-sensitive linker and a disulfide bond, which responds to tumor-overexpressing MMP-2 and GSH at high levels, and WPH, stimulating tumor penetration and acid-responsive drug release by modifying cell-penetrating peptides and polymerizing L-histidine, with prominent features including longer circulation time, better tumor penetration and accumulation, and efficient escape from lysosomes. Finally, PTX released in the tumor cell microenvironment was eight times that discharged in the physiological environment, and significant antitumor effects were achieved.^[360]

Because of the lysosomal sequestration of drugs, MDR often emerges, which is primarily mediated by drug efflux transporter proteins. Induction of lysosomal membrane damage and permeabilization has attracted attention as a potential therapeutic strategy in cancer treatment.^[361–363] Hou et al. synthesized self-condensation prodrug-nanoplatform (LTSPN)

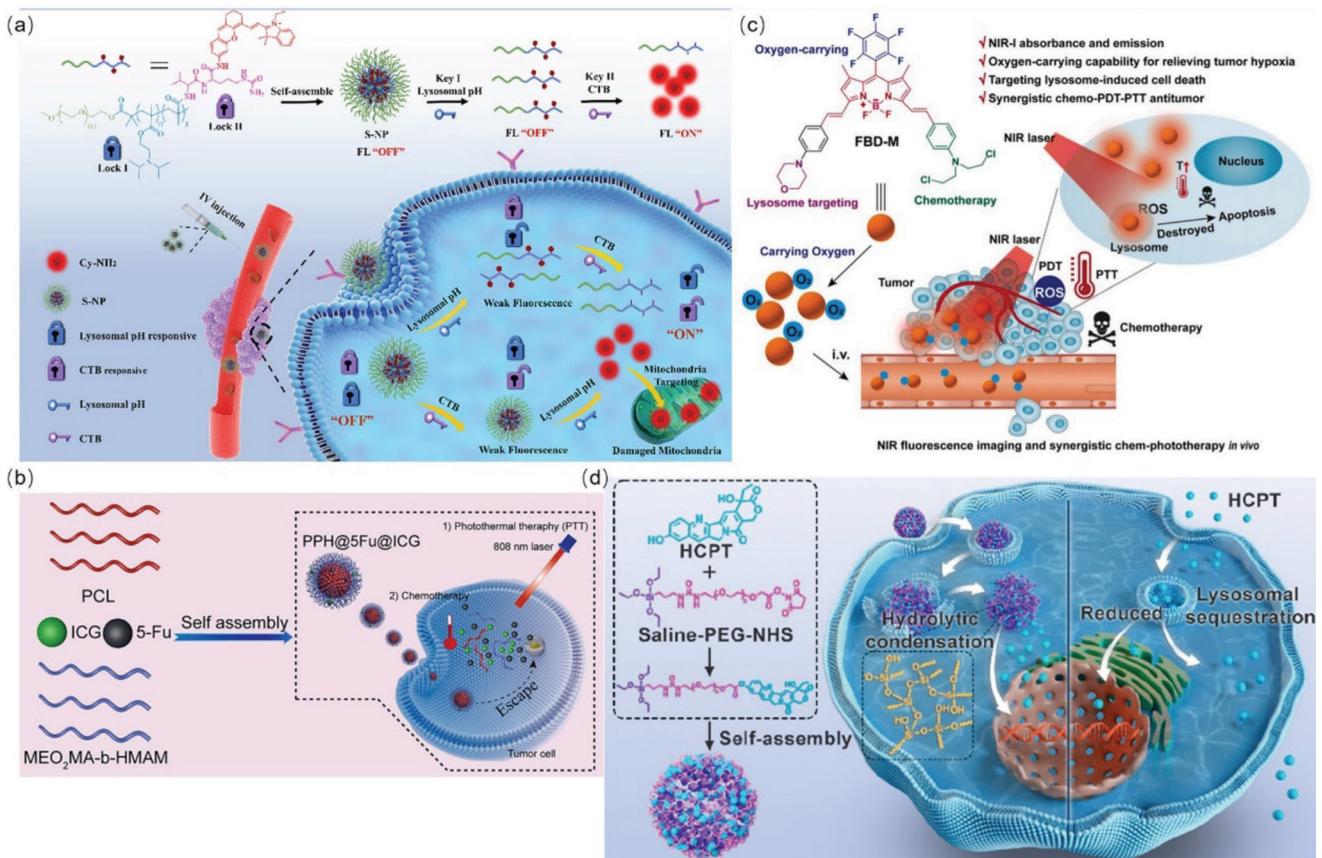


Figure 11. a) Schematic of a dual-locking nanoprobe based on hemicyanine for orthogonal stimuli of lysosomal pH (first “lock”)- and CTB (second “lock”)-triggered precise tumor imaging and therapy. Reproduced with permission.^[347] Copyright 2021, Elsevier B.V. b) Schematic of the preparation of PPH@5Fu@ICG. Reproduced under the terms of the Creative Commons CC BY License.^[356] Copyright 2022, The Authors, published by Wiley Periodicals LLC. c) Schematic of an O-carrying and lysosome-targeting NIR BODIPY derivative for bioimaging and better multimodal cancer therapy. Reproduced with permission.^[359] Copyright 2023, Elsevier B.V. d) Schematic of the destruction of the integrity of the lysosomal membrane by a lysosomal-targeting self-condensation prodrug nanoplateform (LTSNP). Reproduced with permission.^[364] Copyright 2022, American Chemical Society.

system for lysosome targeting. In this nanomaterial, hydroxycamptothecin (HCPT)-silane conjugates self-assembled into silane-based nanoparticles that can accurately target tumor cells and disrupt the integrity of the lysosomal membrane, thus reversing lysosome-mediated drug resistance (Figure 11d).^[364] Yang et al. developed an amphiphilic siRNA-PS conjugate, siPLK1-NB, consisting of a cationic PS (NB-Br) and polo-like kinase 1 (PLK1) siRNA, which self-assembled into NPs (siPLK1-NB NPs); siPLK1-NB NPs demonstrated effective cell endocytosis and tumor-specific accumulation, disrupted lysosome membrane structure, facilitated siRNA escape from lysosomes after localization inside tumor cell lysosomes, and induced siPLK1-NB NP-mediated downregulation of PLK1 expression and photodynamic killing effects under light irradiation both *in vitro* and *in vivo*.^[365]

Nanocarrier systems are promising for targeted therapeutics; however, their antitumor effects are hindered by the entrapment of these systems in endo/lysosomal compartments after endocytosis.^[366] To overcome this challenge, advanced nanocarrier systems are being developed to alter the unique lysosomal environment characterized by acidic pH, enzymes (CTB, sulfatase, and GLU), and photochemical internalization. For example, the esterase-activated DM nanoprodrug created for cancer cell PDT

consists of a hydrolyzable ester linkage connecting a diiodine-substituted fluorogenic malachite green derivative (MG-2I) and the phototherapeutic agent DPP-OH. These nanoplatforms exhibit pH-responsive behaviors in acidic lysosomes, enabling esterase-mediated hydrolysis and release of MG-2I and DPP-OH. The DM nanoprodrug induces lysosomal and mitochondrial damage, optimizing photoablation efficacy and demonstrating potential for enhancing targeted cancer treatment using nanocarrier systems.^[367] To counteract the self-protection mechanisms of lysosomal membranes in response to ROS, Chen et al. developed a lysosome-targeted ROS inducer: N-(3-aminopropyl) morpholine-grafted cross-linked lipoic acid vesicles loaded with vitamin C (VC@^{N3AM} cLAVs). These nanoplatforms demonstrated considerable accumulation in lysosomes and transformed into two redox couples, that is, LA/DHLA (dihydrolipoic acid, the reduced form of LA) and VC/DHA (dehydroascorbic acid, the oxidized form of VC), facilitated by lysosomal GSH. This conversion resulted in the generation of a substantial amount of H₂O₂ via pro-oxidant Fe transformation, which was further amplified via cyclic redox reactions. The formed H₂O₂ was efficiently converted to highly toxic •OH, thereby augmenting ROS production and inducing irreversible cell death in tumor cells.^[368]

6. Golgi Apparatus-Targeting Strategies in Tumor Diagnosis and Treatment

Mutations in Golgi-resident protein genes cause diseases.^[369] Accumulating studies have revealed that dysfunction of the Golgi apparatus is associated with crucial cellular processes, including mitosis, DNA repair, stress responses, autophagy, apoptosis, motility, metabolism, and immune evasion, in cancer initiation and progression.^[370–371] Many altered Golgi proteins, such as Golgi structural proteins, trafficking proteins, glycosylation enzymes, and ion channels, have been identified as hallmarks for cancer diagnosis.^[372–375] Moreover, targeting Golgi apparatus proteins associated with malignant cancer phenotypes has provided promising strategies for treating cancers.^[376–377]

6.1. Golgi Apparatus-Targeting Nanoprobes for Cancer Diagnosis

Aberrant Golgi dynamics, for instance, changes in Golgi orientation and morphology, have a close relationship with the microenvironments and immune landscapes of tumors.^[378–379] Owing to the significant progression of imaging strategies (e.g., cryo-electron microscopy and tomography), researchers can better clarify Golgi morphology and its functions^[380] and *in situ* AFM.^[381] In recent decades, super-resolution confocal microscopy and fluorescent probes have facilitated live and long-term imaging of the Golgi apparatus, revealing details of membrane traffic events.^[382–383] Fluorophore probes, including lectin conjugates, lipophilic dyes, protein transport-affecting drugs, and specific Golgi-resident protein antibodies, for the Golgi have been extensively reviewed.^[384] NPs have emerged as valuable tools for designing Golgi-targeting probes. For example, Wei et al. constructed orange-emissive levorotatory CQDs (L-CQDs) with Golgi apparatus-targeting and imaging capabilities; L-CQDs demonstrated outstanding biocompatibilities, low toxicities, and fluorescence stabilities for both *in vitro* and *in vivo* Golgi apparatus-targeted imaging.^[385] Rong et al. designed a simple Golgi-targeting fluorescent probe, GT-GSH, for accurate detection of GSH in the Golgi, enabling monitoring of tumor cell occurrence and development and providing a novel approach for precise cancer treatment.^[386] (**Figure 12a**). Additionally, Fortibui et al. created a Golgi apparatus-targeting probe based on naphthalimide-based fluorescent molecules, which exhibited a rapid response to FA at room temperature and facilitated intense fluorescence imaging of live BC cells upon FA exposure. Importantly, the presence of phenylsulfonamide enabled visualization of dynamic changes in the targeted Golgi apparatus, offering an early diagnostic strategy for cancer cells^[387] (**Figure 12b,c**).

6.2. Golgi Apparatus-Targeting NPs for Cancer Therapy

Disruptions in Golgi function have been utilized as a strategy to sensitize cancer cells to chemotherapy.^[388] Golgi-targeted nanodrug delivery systems offer a promising approach for cancer treatment, demonstrating high specificities, low-dose administrations, and less side effects.^[389] For instance, Li et al. designed chondroitin sulfate-based prodrug NPs capable of delivering chlorin e6 (Ce6) and retinoic acid (RA) to the Golgi

apparatus of tumor cells, effectively reducing PDT-mediated immunosuppression^[390] (**Figure 12d**). A precise Golgi-targeted delivery system has been developed by coupling ricin A chain (RTA) to CDs, enabling efficient internalization and cytoplasmic delivery of RTA, thus allowing RTA to exert cytotoxicity while avoiding lysosomal degradation.^[391] Furthermore, Chen et al. created hybrid erythrocyte and tumor CM-coated NPs (Hyb-NPs) loaded with monensin, which not only prolonged the circulation time of monensin, but also exhibited recognition and cytotoxicity against primary, circulating, and colonized tumors, thereby significantly reducing spontaneous metastasis in an orthotopic BC model.^[392]

7. CM-Targeting Strategies for Cancer Diagnosis and Therapy

7.1. CM-Targeting Probes for Cancer Diagnosis

CMs, serving as the protective barriers of cells, are closely associated with numerous physiological and pathological processes. CMs of different cell types demonstrate different specific receptors, ligands, and characteristics, particularly in the cases of tumor cells, which are substantially influenced by the interplay between tumor cells and their environments.^[12,393–394] Various strategies targeting the tumor CM have been established for cancer diagnosis and therapy. These strategies involve the recognition of specific cell surface proteins or inherent differences between CM properties such as polarity and viscosity, which arise from the TME.^[395–396] For example, CD44 is a cancer stem cell marker in several cancer types,^[397] and CD44-targeted NPs exhibit potent antitumor effects.^[398]

Many CM-targeting probes based on nanomaterials have been designed for cancer diagnosis.^[399] Due to the significant impact of TME heterogeneity on tumor progression and therapeutic response,^[400] the development of microenvironment-sensitive probes with excellent CM-targeting abilities can uncover fundamental membrane properties.^[401] Li et al. devised a viscosity-responsive CM probe, named TPA-S. This probe demonstrates sensitivity to changes in viscosity and remains non-fluorescent in low-viscosity environments; in contrast, it exhibits high emission capabilities in high-viscosity environments. Owing to this unique property, this probe effectively targets and identifies cancer CMs based on an elevation in membrane viscosity associated with tumorigenesis.^[402]

Considering the difference between the polarities of normal and tumor CMs, Li et al. have constructed a polarity-sensitive CM probe, COP, which contains a coumarin unit, pyridine salt unit, and quaternary ammonium salt unit. COP demonstrates targeted binding to CMs and high sensitivity toward polarity changes, enabling selective labeling of cancer CMs with low polarities.^[403] Wu et al. created polarity-sensitive fluorescent probes, Mem-C1C18 and Mem-C18C18, with excellent CM-targeting abilities and fluorescence lifetimes responsive to environmental polarity. Mem-C1C18 exhibited efficacy in evaluating ferroptosis.^[404] These studies highlight the potential for developing highly sensitive membrane probes to selectively visualize tumors, thereby offering a new avenue for cellular-level tumor diagnosis. Feng et al. designed two polarity-sensitive probes, MEMs, for specific visualization of cancer CMs. These probes, composed of

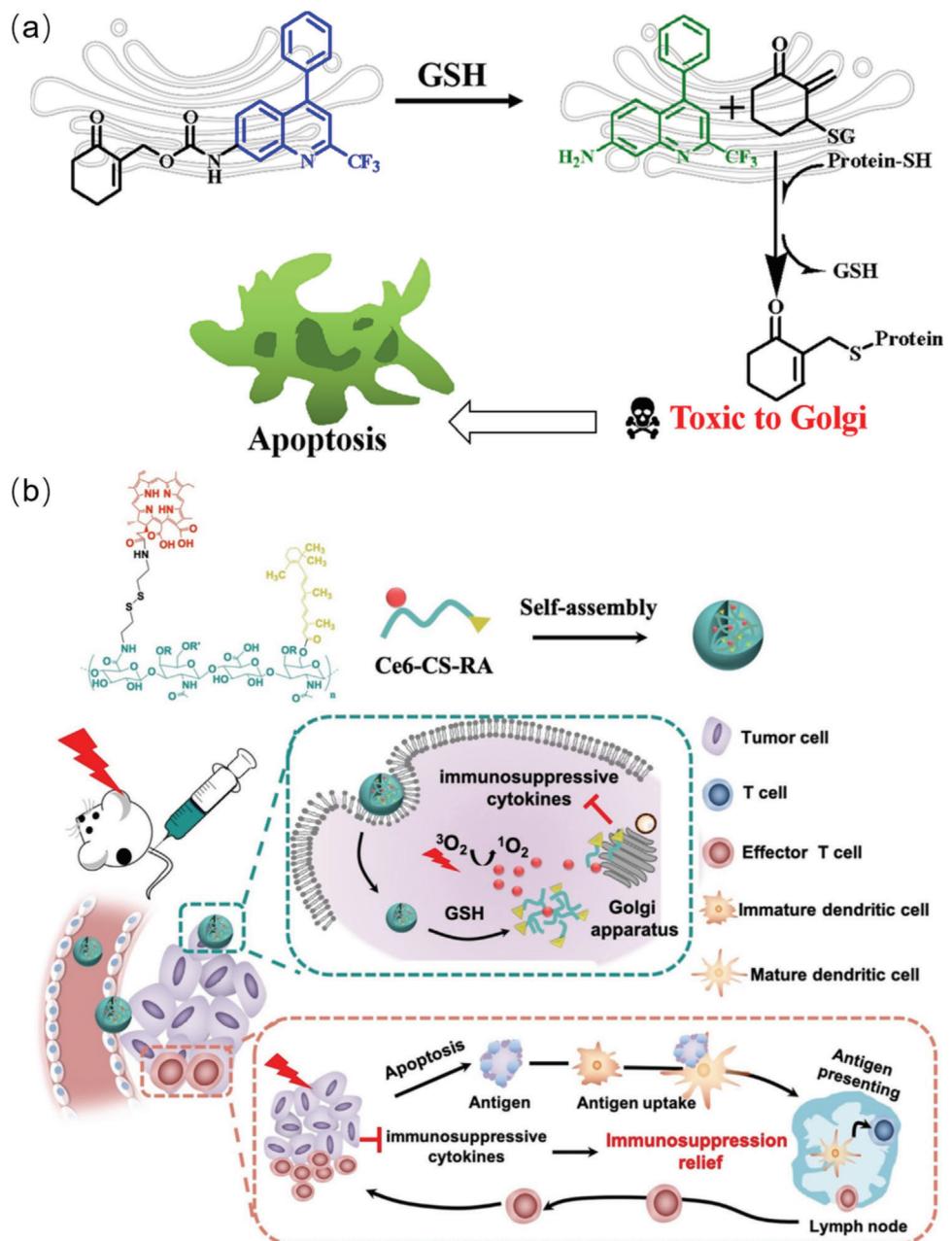


Figure 12. a) Schematic of the synthesis of the fluorescent probe GT-GSH for targeting glutathione in the Golgi apparatus. Reproduced with permission.^[386] Copyright 2021, American Chemical Society. b) Schematic of the in vivo application of the Golgi apparatus-targeting prodrug Ce6-CS-RA nanoparticles for enhanced photodynamic immunotherapy. Reproduced with permission.^[390] Copyright 2022, Acta Materialia Inc.

tetrahydroquinoxaline coumarin amide fluorophores and quaternary ammonium groups for high water solubility and CM targeting ability, demonstrated a wide linear range for polarity detection^[405] (Figure 13a–d).

Another group of CM-targeting nanoprobe, including the D peptide ligand [¹⁸F]AlF-NOTA-^DVAP (used for recognizing GRP78 expressed on the cell surface of BC)^[406] and the [¹⁸F]AlF-labeled ODAP-urea-based prostate-specific membrane antigen probe,^[407] was synthesized that could detect particular proteins on the surfaces of CMs.^[408] According to the experimental re-

sults, these probes exhibit high specificities and binding affinities to cell-surface targets and can be employed for cancer imaging.

Designing fluorescent probes with low susceptibilities to photobleaching is necessary for meeting the clinical needs for tumor imaging.^[409] Liu et al. developed self-assembled nanoprobe using Ru(II)-coumarin complexes comprising Ru, 1,10-phenanthroline, and coumarin 6. These nanoprobe demonstrated outstanding CM-targeting and imaging capabilities, outperforming commercial Dil by exhibiting superior

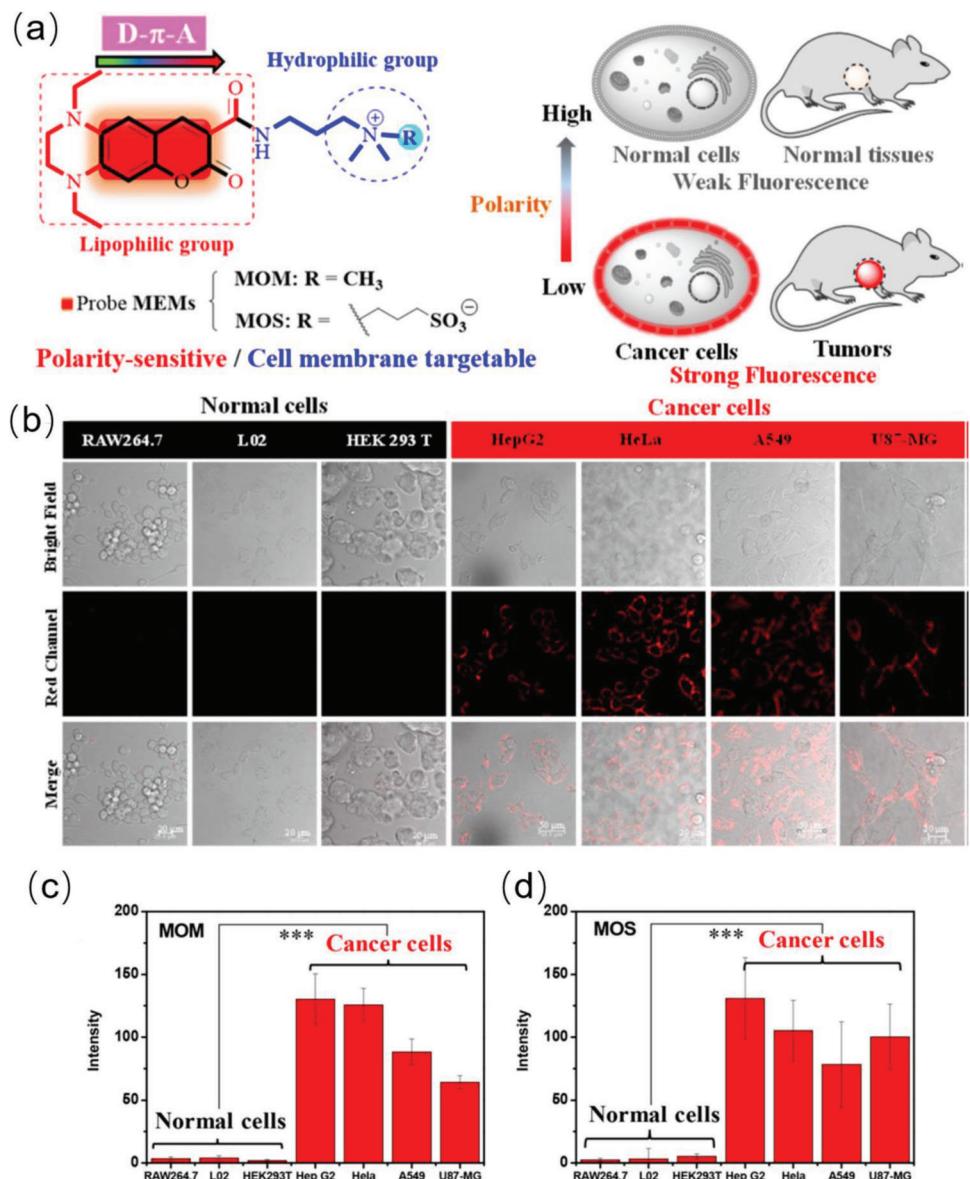


Figure 13. a) Schematic of probe MEMs for discrimination of cancer cells/tissues from normal cells/tissues. b) Confocal images of normal and cancer cells after incubation with MOM. c,d) Fluorescence intensity. Reproduced with permission.^[405] Copyright 2022, American Chemical Society.

stabilities for long-term and high signal-to-noise ratio imaging.^[410] Wang et al. engineered a photostable cascade-activatable peptide system, referred to as the target reaction-induced aggregation peptide (TRAP) system, which achieved prolonged and stable imaging of bladder cancer via *in situ* formation of polypeptide-based nanofibers on the CM. The probe consisted of a target peptide that recognized CD44v6 for bladder cancer cell targeting and a reaction-induced aggregation peptide that enhanced hydrophobicity via a click reaction with TP, producing nanofibers and nanonetworks. This resulted in prolonged retention of the probe on the CM and considerably improved photostability. The TRAP system demonstrated effective and stable imaging of bladder cancer, as validated by high-performance identification of human bladder cancer using *ex vivo* bladder tumor tissues^[411] (Figure 13e).

7.2. CM-Targeting NPs for Cancer Therapy

In recent years, targeted tumor CM damage therapeutics have emerged as a highly interesting direction in precision cancer therapy.^[412] Xu et al. have conjugated the PS chlorin e6 with PEG followed by assembly with the acid-sensitive polymer poly(2-azepane ethyl methacrylate) (PAEMA) to form PEG-Ce6@PAEMA. The acidic microenvironment of tumor tissue triggers the protonation of the PAEMA core, leading to the disassembly of PEG-Ce6@PAEMA and subsequent release of PEG-Ce6. PEG-Ce6 can selectively anchor to the membranes of cancer cells, facilitating efficient membrane-targeted tumor ablation under 660 nm laser irradiation.^[413] Zhang et al. have reported an enzyme-driven CM-targeting chimeric peptide, PpIX-C6-PEG8-KKKKKSKTKC-OMe (PCPK). This chimeric peptide

induces rapid release of damage-associated molecular patterns via tumor CM damage. The CM-targeting ability of PCPK is facilitated by intracellular protein-farnesyl transferase, which allows PCPK to specifically target and anchor to the CM. Upon exposure to 660 nm light, PCPK generates cytotoxic ROS, disrupting the structure of the CM. This causes tumor ablation and triggers an antitumor immune response. The membrane-targeted PDT described herein holds significant potential for synergistic collaboration with IMT for antitumor applications.^[414] Fan et al. developed an imaginative peptide nanomedicine (PNpC) that can be utilized as an immunogenic cell death (ICD) initiation strategy in cancer treatment. This functional material was designed based on the fragment CM11 of cecropin, which can effectively disrupt the CM via its specific α -helical structure. With the help of the high levels of alkaline phosphatase (ALP) on the tumor CM, PNpC self-assembles in situ and transforms from nanoparticles to nanofibers, thus reducing the cellular internalization of the nanomedicine and expediting CM11 and tumor CMs interaction. PNpC showed potent tumor cell-killing abilities both in vitro and in vivo by triggering ICD, enhancing the maturation of DCs, and facilitating the presentation of tumor-associated antigens. Therefore, the infiltration of CD8⁺ T cells increased within the tumors.^[415]

Cancer CM-wrapped NPs can also increase tumor targeting via homologous membrane and are promising for improved drug delivery, localized phototherapy, intensified imaging, and potent IMT.^[416] Numerous CMs, including red blood, platelet, mesenchymal stem, and cancer CMs, have been utilized for this biomimetic approach.^[417] For instance, Jiang et al. fabricated a biomimetic NP platform using a cancer CM coating expressing a costimulatory marker, which promoted tumor antigen-specific immune responses and activated primed T cells for effective tumor growth control.^[418] Cui et al. designed functional NPs comprising an aggregation-induced emission molecule (DHTDP) that enabled NIR-II fluorescence emission and efficient photothermal conversion. These DHTDP NPs camouflaged with cancer CMs, enhancing the delivery efficiency and homologous targeting ability^[419] (Figure 13f). Coating NPs with macrophage or neutrophil CMs endows the NPs with significant properties such as prolonged circulation, high targeting abilities, better cellular interactions, gradual drug release, and low systemic toxicity.^[420–421] Zhao et al. have developed a CM biomimetic nanosystem (RBC-H@DOX/3-HF@MSN) by encapsulating a mixed membrane of HepG2 cells (human liver cancer cell line) and red blood cells around NPs and loaded the hollow cavities of MSNs with the chemotherapeutic drug DOX and photoCORMs 3-HF. Modification of the mixed membrane imparts the NPs with homotypic tumor-targeting abilities, eventually resulting in precise light-triggered cancer cell ablation.^[422]

8. Multi-Organelle-Targeting Strategies for Cancer Therapy

Combination therapy demonstrates promising potential for future cancer treatment because of its synergistic effects, low non-specific toxicity, and ability to overcome MDR.^[423,424] Targeting multiple organelles using smart nanoplateforms leads to better antitumor effects. For example, Chen et al. fabricated DGLipo

NPs with DOX intercalated in the DNA duplex, cyclopeptide RA-V in pH-sensitive liposomal shells, and dual modifications of c(RGDFK) and MPP. These NPs sequentially delivered drugs to lysosomes and mitochondria, resulting in better therapeutic outcomes for multidrug-resistant tumors.^[425] Similar strategies have been successfully applied to other cancers.^[426] Zhu et al. created carrier-free theranostic NPs self-assembled from aurantiamide acetate (Aa), scutebarbatine A (SA), and palmitin (P), which are named ASP NPs. The designed NPs exhibited EPR effects and targeted mitochondria and lysosomes at tumor sites. The combination of Aa, SA, and P synergistically improved the uptake of ASP NPs by cancer CMs, inducing mitochondrial apoptosis, inhibiting TNBC via ferroptosis, and upregulating p53.^[427]

Mitochondria-targeted therapies demonstrate limitations due to the adaptive rescue capacities of nuclei.^[428] To overcome this issue, a strategy combining targeting of both mitochondria and the nucleus has been developed for better antitumor effects.^[429] Yao et al. combined XPO1 inhibitor KPT-330 NPs with mitochondria-targeting lonidamine (TPP-LND, TL) NPs in a 1:4 ratio (KPT:TL), and the resulting material exhibited the best synergistic effect in suppressing the proliferation and metastasis of 4T1 BC cells.^[430]

9. Conclusions and Future Prospects

Subcellular targeting strategy demonstrates substantial potential in the next generation of cancer therapy and has gradually emerged as a promising approach in personalized cancer treatment. Although controlled delivery at the subcellular organelle level has been realized, its complete utilization in current medical practice remains underexplored. To expedite the future clinical applications of subcellular targeted cancer therapy, continuous monitoring of the clinical trials of subcellular targeted cancer treatment and exploration of interdisciplinary applications of novel techniques and methodologies are imperative.

The TME undergoes complex stromal and evolutionary changes, influenced by intricate interactions between cells and their surroundings. Overcoming immune-suppressive environments, particularly in solid tumors, remains challenging and necessitates further exploration of the temporal and spatial control exerted by functional materials at the tumor site. On the one hand, a comprehensive elaboration of the behaviors and physicochemical properties of NPs and their impacts on regulated drug release and therapeutic mechanisms needs further attention. On the other hand, systematic exploration of the intracellular behaviors of NPs is crucial for understanding optimal material characteristics and overcoming biological barriers. Moreover, the heterogeneities of tumors, intricate interactions within the TME, and the network effects of subcellular interactions considerably influence the responses of tumors to different treatments and drug efficacy in cancer patients. Comprehensive exploration of the complex mechanisms of tumor cells and temporal and spatial properties of functional materials at the tumor sites is of significant importance in overcoming immune suppression and improving treatment outcomes.

Medical imaging techniques, including computed tomography, PET, MRI, photoacoustic imaging, and optical super-resolution imaging, have rapidly advanced from the organ to subcellular nanoscale levels. Integration of imaging techniques with functional materials not only enables real-time

monitoring of the therapeutic process, but also provides a scientific basis for optimizing drug delivery and treatment strategies by improving the tracking of spatiotemporal events at the subcellular level. Specifically in the context of tumor treatment, optical imaging techniques targeting subcellular structures offer valuable information about the localizations, distributions, and interactions of functional materials within subcellular compartments. Researchers can visualize and analyze dynamic processes, such as drug delivery, cellular uptake, and intracellular transport, in real time. Optical super-resolution imaging techniques represent a promising convergence point for the development of functional materials designed for “targeting subcellular organelles in tumor cells.”

Optical super-resolution imaging techniques, including structured illumination microscopy (SIM), STORM, and stimulated emission depletion (STED) microscopy, have revolutionized the field of optical molecular imaging by surpassing the diffraction limit (200 nm) and enabling imaging at the nanoscale.^[431] These techniques have opened up new possibilities for investigating the behaviors of functional materials in tumor treatment, unveiling the intricate details of TMEs, and shedding light on the underlying mechanisms of therapeutic effects. Furthermore, one of the key advantages of optical super-resolution technology is its compatibility with functional materials. Using specific labeling strategies, such as fluorescent probes and NPs, researchers can track the localizations and behaviors of functional materials in real time with high precision, offering valuable insights for optimizing the designs and performances of functional materials. For example, SIM facilitates fast and high-throughput imaging, rendering it suitable for screening and characterizing large libraries of functional materials.^[432] In contrast, STORM and STED microscopy provide exquisite spatial resolution, allowing researchers to examine the intricate structures and dynamics of functional materials at the nanoscale.^[433,434] These techniques pave the way for the development of advanced theranostic platforms by integrating imaging and therapeutic functionalities into a single system. In conclusion, optical super-resolution technology has emerged as a powerful tool for investigating functional materials in tumor treatment. Its ability to visualize and analyze subcellular processes at the nanoscale offers valuable insights for optimizing the designs and performances of functional materials. By pushing the boundaries of optical imaging, these techniques exhibit significant promise for advancing our understanding of tumor biology and improving the efficacies of therapeutic strategies.

Artificial intelligence (AI) technology has revolutionized various fields, and its application in the development of functional materials, particularly for tumor treatment, demonstrates considerable promise. AI methods, for instance, machine learning and deep learning algorithms, have the potential to accelerate the discovery, design, and high-throughput advancement of functional materials with high therapeutic efficacies and targeting abilities.^[435] For tumor treatment, the development of functional materials requires a systematic understanding of the complex interactions between materials, cells, and the TME. AI algorithms can analyze large datasets, including genomic, proteomic, and clinical data, to identify key biomarkers, molecular targets, and therapeutic pathways.^[436,437] This information can guide the rational design of functional materials with better specificities and

efficiencies in tumor targeting. AI can also facilitate the discovery of novel functional materials via computational simulations and virtual screening.^[438,439] Using AI algorithms, researchers can rapidly screen a vast chemical space, predict the properties and behaviors of materials, and determine potential candidates for further experimental validation. This approach significantly accelerates the material discovery process and reduces the cost and time required for experimental synthesis and testing. Furthermore, AI techniques enable the development of predictive models for drug delivery and release systems. By integrating computational modeling and machine learning, researchers can optimize the design parameters, such as particle size, surface modifications, and release kinetics, of drug delivery systems to achieve controlled and targeted drug delivery.^[437] This personalized approach enhances treatment efficacy while minimizing side effects. In conclusion, AI technology has extensive potential in the advancement of functional materials for tumor treatment. Its ability to analyze large datasets, facilitate material discovery, and optimize drug delivery systems can substantially accelerate the development of effective and personalized therapeutic strategies. By combining AI with traditional experimental methods, researchers can unlock new possibilities for the design and development of functional materials with better therapeutic efficacies and targeting abilities.

Clinical application and translation of functional materials in cancer treatment face several potential challenges. Attention should be paid to the selection of appropriate drug delivery and release systems during clinical translation. A comprehensive evaluation of the stabilities, biodegradabilities, and drug release kinetics of functional materials in *in vivo* applications is required. To achieve efficient transport and release of functional materials, appropriate drug loading, release rates, and targeting specificity should be considered. Additionally, thorough investigations of the biological behaviors, including metabolism, distribution, and excretion, of functional materials are necessary. Owing to the heterogeneities and complexities of tumors, the selection of suitable animal models is crucial for assessing the efficacies and safeties of functional materials. For instance, although mouse models are widely used in basic research, their anatomical structures, immune systems, and metabolic processes differ from those of humans. Therefore, during animal experiments, the use of animal models, such as large animal models and tumor xenograft models, that are more appropriate for the tumor type and biological characteristics should be considered. Furthermore, to obtain clinically relevant outcomes, sample size and experimental design should be carefully considered during large-scale animal experiments. Suitable experimental design and statistical analysis can enhance the reliability and reproducibility of experimental results while reducing biases. Generally, the clinical translation of functional materials for cancer treatment requires careful consideration of various factors including appropriate drug delivery and release systems, comprehensive evaluation of biological behaviors, and suitable animal models. Once these challenges are addressed, functional materials can be utilized to improve the efficacy and safety of cancer treatment, ultimately benefiting patients.

In summary, herein, a systematic and comprehensive overview of the research progress in subcellular organelle-targeted cancer therapy based on functional nanomaterials is provided. This

review serves as an excellent cutting-edge guide for researchers in the field of subcellular organelle-targeted cancer therapy. Although subcellular targeted cancer therapy strategies have demonstrated considerable potentials, they still face significant challenges that need to be overcome before subcellular-targeting drugs can enter clinical trials or even clinical applications. However, we remain optimistic about achieving significant progress in the efficacy of cancer therapy via interdisciplinary collaborations encompassing materials science, pharmaceutics, biology, informatics, and clinical medicine. We believe that this powerful technology possesses extensive potential to revolutionize cancer treatment at the intersection of biology, nanomaterials, and medicine. By addressing the challenges and limitations of current strategies, researchers can develop more effective and targeted cancer therapies that improve patient outcomes and quality of life. With continuous research and development, the subcellular organelle-targeted cancer therapy based on functional nanomaterials may become a standard approach in cancer treatment, bringing us one step closer to a world without cancer.

Acknowledgements

Y.C., Z.Q., and Q.J. contributed equally to this work. The research was funded by the National Natural Science Foundation of China: (81502087, 31600692), the Natural Science Fund of Hubei Province: 2023AFB926, Hubei Province health and family planning scientific research project: (WJ2019H349, WJ2023M138).

Conflict of Interest

The authors declare no conflict of interest.

Keywords

cancer therapy, functional materials, nanomedicine, precise therapy, subcellular organelles

Received: May 29, 2023

Revised: July 26, 2023

Published online:

- [1] D. Gambarotto, F. U. Zwettler, M. Le Guennec, M. Schmidt-Cernohorska, D. Fortun, S. Borgers, J. Heine, J.-G. Schloetel, M. Reuss, M. Unser, E. S. Boyden, M. Sauer, V. Hamel, P. Guichard, *Nat. Methods* **2019**, *16*, 71.
- [2] T. Tamura, A. Fujisawa, M. Tsuchiya, Y. Shen, K. Nagao, S. Kawano, Y. Tamura, T. Endo, M. Umeda, I. Hamachi, *Nat Chem Biol.* **2020**, *16*, 1361.
- [3] R. Pelletier, D. I. Danylchuk, H. Benissa, F. Broch, R. Vauchelles, A. Gautier, A. S. Klymchenko, *Anal Chem.* **2023**, *95*, 8512.
- [4] J. R. Inigo, D. Chandra, *J Hematol Oncol.* **2022**, *15*, 98.
- [5] K. G. Roth, I. Mambetsarev, P. Kulkarni, R. Salgia, *Trends Mol Med.* **2020**, *26*, 119.
- [6] X. Chen, J. R. Cubillos-Ruiz, *Nat. Rev. Cancer* **2021**, *21*, 71.
- [7] S. Banerjee, W. Zhang, *ChemBioChem* **2018**, *19*, 2341.
- [8] M. E. Kreft, A. A. Mironov, S. Hudoklin, *Histochem Cell. Biol.* **2022**, *158*, 229.
- [9] S. Kumar, M. Sánchez-Álvarez, F.-N. Lolo, F. Trionfetti, R. Strippoli, M. Cordani, *Cells* **2021**, *10*, 2752.

- [10] Z. Zhang, P. Yue, T. Lu, Y. Wang, Y. Wei, X. Wei, *J Hematol Oncol.* **2021**, *14*, 79.
- [11] W.-J. Wang, L.-Y. Li, J.-W. Cui, *Epigenetics Chromatin* **2020**, *13*, 49.
- [12] W. Fei, J. Yan, X. Wu, S. Yang, X. Zhang, R. Wang, Y. Chen, J. Xu, C. Zheng, *Theranostics* **2023**, *13*, 2471.
- [13] M. Han, E. A. Bushong, M. Segawa, A. Tiard, A. Wong, M. R. Brady, M. Momcilovic, D. M. Wolf, R. Zhang, A. Petcherski, M. Madany, S. Xu, J. T. Lee, M. V. Poyurovsky, K. Olszewski, T. Holloway, A. Gomez, M. S. John, S. M. Dubinett, C. M. Koehler, O. S. Shiraihi, L. Stiles, A. Lisberg, S. Soatto, S. Sadeghi, M. H. Ellisman, D. B. Shackelford, *Nature* **2023**.
- [14] J. P. Grieco, M. E. Allen, J. B. Perry, Y. Wang, Y. Song, A. Rohani, S. L. E. Compton, J. W. Smyth, N. S. Swami, D. A. Brown, E. M. Schmelz, *Front Oncol.* **2021**, *10*, 600113.
- [15] H. Fang, Y. Chen, S. Geng, S. Yao, Z. Guo, W. He, *Anal Chem.* **2022**, *94*, 17904.
- [16] L. Qiao, X. Shao, S. Gao, Z. Ming, X. Fu, Q. Wei, *Colloids Surf B Biointerfaces* **2021**, *208*, 112046.
- [17] M. Fang, X. Zhou, S. Wang, Y. Yang, Y. Cheng, B. Wang, X. Rong, X. Zhang, K. Xu, Y. Zhang, S. Zheng, *Spectrochim Acta A Mol Biomol Spectrosc.* **2023**, *298*, 122791.
- [18] L. Yang, P. Gu, A. Fu, Y. Xi, S. Cui, L. Ji, L. Li, N. Ma, Q. Wang, G. He, *Talanta* **2023**, *265*, 124862.
- [19] G. Paradies, V. Paradies, F. M. Ruggiero, G. Petrosillo, *Cells* **2019**, *8*, 728.
- [20] M. Wang, R. J. Kaufman, *Nature* **2016**, *529*, 326.
- [21] J. Root, P. Merino, A. Nuckols, M. Johnson, T. Kukar, *Neurobiol Dis.* **2021**, *154*, 105360.
- [22] M. Wei, Z. Zhu, J. Wu, Y. Wang, J. Geng, Z.-H. Qin, *Cell Signal.* **2019**, *63*, 109375.
- [23] K.-I Lee, C.-C. Su, C.-Y. Yang, D.-Z. Hung, C.-T. Lin, T.-H. Lu, S.-H. Liu, C.-F. Huang, *Toxicol In Vitro* **2016**, *36*, 142.
- [24] Z. Feng, Y. Xia, T. Gao, F. Xu, Q. Lei, C. Peng, Y. Yang, Q. Xue, X. Hu, Q. Wang, R. Wang, Z. Ran, Z. Zeng, N. Yang, Z. Xie, L. Yu, *Cell Death Dis.* **2018**, *9*, 1006.
- [25] A. Pawlik, M. A. Szczepanski, A. Klimaszewska-Wisniewska, L. Gackowska, A. Zuryn, A. Grzanka, *Acta Histochem.* **2016**, *118*, 784.
- [26] K. Miyamoto, T. Minegaki, S. Hirano, I. Hayashi, M. Tsujimoto, K. Nishiguchi, *Anticancer Res.* **2020**, *40*, 813.
- [27] R. Lamb, M. Fiorillo, A. Chadwick, B. Ozsvari, K. J. Reeves, D. L. Smith, R. B. Clarke, S. J. Howell, A. R. Cappello, U. E. Martinez-Outschoorn, M. Peiris-Pagès, F. Sotgia, M. P. Lisanti, *Oncotarget* **2015**, *6*, 14005.
- [28] P. C. Thakur, J. L. Miller-Ocuin, K. Nguyen, R. Matsuda, A. D. Singhi, H. J. Zeh, N. Bahary, *J Transl Med.* **2018**, *16*, 190.
- [29] N. T. Hanke, L. L. Garland, A. F. Baker, *J Cancer Res Clin Oncol.* **2016**, *142*, 549.
- [30] S. Periyasamy-Thandavan, W. H. Jackson, J. S. Samaddar, B. Erickson, J. R. Barrett, L. Raney, E. Gopal, V. Ganapathy, W. D. Hill, K. Bhalla, P. V. Schoenlein, *Autophagy* **2010**, *6*, 19.
- [31] R.-Y. Yu, L. Xing, P.-F. Cui, J.-B. Qiao, Y.-J. He, X. Chang, T.-J. Zhou, Q.-R. Jin, H.-L. Jiang, Y. Xiao, *Biomater Sci.* **2018**, *6*, 2144.
- [32] S. Marastoni, A. Madariaga, A. Pesic, S. N. Nair, Z. J. Li, Z. Shalev, T. Ketela, I. Colombo, V. Mandilaras, M. Cabanero, J. P. Bruce, X. Li, S. Garg, L. Wang, E. X. Chen, S. Gill, N. C. Dhani, W. Zhang, M. Pintilie, V. Bowering, M. Koritzinsky, R. Rottapel, B. G. Wouters, A. M. Oza, A. M. Joshua, S. Lheureux, *Cancer Res Commun.* **2022**, *2*, 293.
- [33] V. Jain, S. L. Harper, A. M. Versace, D. Fingerman, G. S. Brown, M. Bhardwaj, M. A. S. Crissey, A. R. Goldman, G. Ruthel, Q. Liu, A. Zivkovic, H. Stark, M. Herlyn, P. A. Girmotti, D. W. Speicher, R. K. Amaravadi, *Cancer Discov.* **2023**, *13*, 454.
- [34] J. Gavini, N. Dommann, M. O. Jakob, A. Keogh, L. C. Bouchez, S. Karkampouna, M. K.-D. Julio, M. Medova, Y. Zimmer, A. M. Schlafli, M. P. Tschan, D. Candinas, D. Stroka, V. Banz, *Cell Death Dis.* **2019**, *10*, 749.

- [35] E.-J. Im, C.-H. Lee, P.-G. Moon, G. G. Rangaswamy, B. Lee, J. M. Lee, J.-C. Lee, J.-G. Jee, J.-S. Bae, T.-K. Kwon, K.-W. Kang, M.-S. Jeong, J.-E. Lee, H.-S. Jung, H.-J. Ro, S. Jun, W. Kang, S.-Y. Seo, Y.-E. Cho, B.-J. Song, M.-C. Baek, *Nat Commun.* **2019**, *10*, 1387.
- [36] S. Datta, T. Sears, G. Cortopassi, K. Woolard, J. M. Angelastro, *Biomed. Pharmacother.* **2021**, *133*, 111058.
- [37] C. W. Schultz, G. A. McCarthy, T. Nerwal, A. Nevler, J. B. Duhadaway, M. D. McCoy, W. Jiang, S. Z. Brown, A. Goetz, A. Jain, V. S. Calvert, V. Vishwakarma, D. Wang, R. Preet, J. Cassel, R. Summer, H. Shaghaghi, Y. Pommier, S. A. Baechler, M. J. Pishvaian, T. Golan, C. J. Yeo, E. F. Petricoin, G. C. Prendergast, J. Salvino, P. K. Singh, D. A. Dixon, J. R. Brody, *Mol Cancer Ther.* **2021**, *20*, 2166.
- [38] T. Liu, C.-F. Xiong, L.-J. Zhang, G.-H. Jiao, H. Shi, J. Feng, X.-Z. Zhang, *Adv. Healthcare Mater.* **2023**, *12*, e2202045.
- [39] F. Servida, D. Lecis, C. Scavullo, C. Drago, P. Seneci, C. Carlo-Stella, L. Manzoni, E. Polli, G. Lambertenghi Deliliers, D. Delia, F. Onida, *Invest New Drugs* **2011**, *29*, 1264.
- [40] M. Mahameed, S. Boukeileh, A. Obiedat, O. Darawshi, P. Dipta, A. Rimon, G. Mclellan, R. Fassler, D. Reichmann, R. Karni, C. Preisinger, T. Wilhelm, M. Huber, B. Tirosh, *Nat Commun.* **2020**, *11*, 1304.
- [41] J.-T. Lin, H. Chen, D. Wang, L. Xiong, J.-Z. Li, G.-H. Chen, G.-B. Chen, *Colloids Surf B Biointerfaces* **2019**, *183*, 110440.
- [42] W. Mao, J. Chen, Y. Wang, Y. Fang, H. Wu, P. He, *Photodiagnosis Photodyn Ther.* **2022**, *40*, 103135.
- [43] W. Zhang, X.-F. Du, B. Liu, C. Li, J. Long, M.-X. Zhao, Z. Yao, X.-J. Liang, Y. Lai, *ACS Nano* **2022**, *16*, 1421.
- [44] R. Wang, X. Li, J. Yoon, *ACS Appl. Mater. Interfaces* **2021**, *13*, 19543.
- [45] J. B. Wenger, S. Y. Chun, D. T. Dang, H. Luesch, L. H. Dang, *Medical hypotheses* **2011**, *76*, 169.
- [46] Z. Li, J. Zou, X. Chen, *Adv. Mater.* **2022**, 2209529.
- [47] Z. He, Y. Zhang, A. R. Khan, J. Ji, A. Yu, G. Zhai, *J Drug Target* **2021**, *29*, 12.
- [48] D. Averbeck, C. Rodriguez-Lafrasse, *Int J Mol Sci.* **2021**, *22*, 11047.
- [49] H. Chen, D. C. Chan, *Cell Metab.* **2017**, *26*, 39.
- [50] L. Sainero-Alcolado, J. Liaño-Pons, M. V. Ruiz-Pérez, M. Arsenian-Henriksson, *Cell Death Differ.* **2022**, *29*, 1304.
- [51] P. K. Kopinski, L. N. Singh, S. Zhang, M. T. Lott, D. C. Wallace, *Nat Rev Cancer.* **2021**, *21*, 431.
- [52] B. N. Whitley, E. A. Engelhart, S. Hoppins, *Mitochondrion* **2019**, *49*, 269.
- [53] R. Rodrigo, N. Mendis, M. Ibrahim, C. Ma, E. Kreinin, A. Roma, S. Berg, J. Blay, P. A. Spagnuolo, *Autophagy* **2019**, *15*, 900.
- [54] M. A. Yapryntseva, P. V. Maximchik, B. Zhivotovsky, V. Gogvadze, *Front Cell Dev Biol.* **2022**, *10*, 947357.
- [55] J. Lee, A. E. Yesilkanal, J. P. Wynne, C. Frankenberger, J. Liu, J. Yan, M. Elbaz, D. C. Rabe, F. D. Rustandy, P. Tiwari, E. A. Grossman, P. C. Hart, C. Kang, S. M. Sanderson, J. Andrade, D. K. Normura, M. G. Bonini, J. W. Locasale, M. R. Rosner, *Nature* **2019**, *568*, 254.
- [56] M. R. McCann, M. V. George De La Rosa, G. R. Rosania, K. A. Stringer, *Metabolites* **2021**, *11*, 51.
- [57] J. Liang, R. Cao, X. Wang, Y. Zhang, P. Wang, H. Gao, C. Li, F. Yang, R. Zeng, P. Wei, D. Li, W. Li, W. Yang, *Cell Res.* **2017**, *27*, 329.
- [58] K. Zoraiz, M. Attique, S. Shahbaz, M. W. Ahmed, M. A. Kayani, I. Mahjabeen, *Future Oncol.* **2021**, *17*, 3561.
- [59] R. Kumar, J. Han, H.-J. Lim, W. X. Ren, J.-Y. Lim, J.-H. Kim, J. S. Kim, *J Am Chem Soc.* **2014**, *136*, 17836.
- [60] K. Vasan, M. Werner, N. S. Chandel, *Cell Metab.* **2020**, *32*, 341.
- [61] T. Rodrigues, L. S. Ferraz, *Biochem Pharmacol.* **2020**, *182*, 114282.
- [62] S. Wang, Q. Zhang, M. Peng, J. Xu, Y. Guo, *Molecules* **2023**, *28*, 1016.
- [63] S. Mukherjee, G. K. Bhatti, R. Chhabra, P. H. Reddy, J. S. Bhatti, *Biomed. Pharmacother.* **2023**, *160*, 114398.
- [64] M.-P. Liu, M. Liao, C. Dai, J.-F. Chen, C.-J. Yang, M. Liu, Z.-G. Chen, M.-C. Yao, *Sci Rep.* **2016**, *6*, 34245.
- [65] T. Yeo, J. Kintner, R. Armand, R. Perez, L. Lewis, *Hum Exp Toxicol.* **2007**, *26*, 911.
- [66] S. T. Ahmadpour, V. Desquiret-Dumas, U. Yikilmaz, J. Dartier, I. Domingo, C. Wetterwald, C. Orre, N. Gueguen, L. Brisson, K. Mahéo, J.-F. Dumas, *Int J Mol Sci.* **2021**, *22*, 9283.
- [67] D. Shah, Ajazuddin, S. Bhattacharya, *J Cancer Res Clin Oncol.* **2023**, *149*, 367.
- [68] J. Yang, Y. Zhou, S. Xie, J. Wang, Z. Li, L. Chen, M. Mao, C. Chen, A. Huang, Y. Chen, X. Zhang, N. U. H. Khan, L. Wang, J. Zhou, *J Exp Clin Cancer Res.* **2021**, *40*, 206.
- [69] M. Nishida, N. Yamashita, T. Ogawa, K. Koseki, E. Warabi, T. Ohue, M. Komatsu, H. Matsushita, K. Kakimi, E. Kawakami, K. Shiroguchi, H. Udon, *J Immunother Cancer* **2021**, *9*, e002954.
- [70] A. Arinno, C. Manechote, T. Khuanjing, B. Ongnok, N. Prathumsap, T. Chunchai, B. Arunsak, S. Kerdphoo, K. Shinlapawittayatorn, S. C. Chattipakorn, N. Chattipakorn, *Biochem Pharmacol.* **2021**, *192*, 114743.
- [71] B. M. El-Fatatty, O. M. Ibrahim, F. Z. Hussien, T. M. Mostafa, *Int J Colorectal Dis.* **2018**, *33*, 1675.
- [72] G. Cheng, J. Zielonka, M. Hardy, O. Ouari, C. R. Chitambar, M. B. Dwinell, B. Kalyanaraman, *Oncotarget.* **2019**, *10*, 3518.
- [73] M. Abueid, R. F. Keyes, D. Mcallister, F. Peterson, I. P. Kadamberi, D. J. Sprague, P. Chaluvally-Raghavan, B. C. Smith, M. B. Dwinell, *iScience* **2022**, *25*, 105670.
- [74] B. Kalyanaraman, *FASEB J.* **2022**, *36*, e22226.
- [75] L. De Beauchamp, E. Hirmonas, G. V. Helgason, *Leukemia* **2022**, *36*, 1.
- [76] V. Infantino, A. Santarsiero, P. Convertini, S. Todisco, V. Iacobazzi, *Int J Mol Sci.* **2021**, *22*, 5703.
- [77] Q. Xu, J. Tu, C. Dou, J. Zhang, L. Yang, X. Liu, K. Lei, Z. Liu, Y. Wang, L. Li, H. Bao, J. Wang, K. Tu, *Mol Cancer* **2017**, *16*, 178.
- [78] Z. Zhang, M. Banerjee, R. E. Davis, B. S. J. Blagg, *Bioorg Med Chem Lett.* **2019**, *29*, 126676.
- [79] B. H. Kang, M. Tavecchio, H. L. Goel, C.-C. Hsieh, D. S. Garlick, C. M. Raskett, J. B. Lian, G. S. Stein, L. R. Languino, D. C. Altieri, *Br. J. Cancer* **2011**, *104*, 629.
- [80] U. Hayat, G. T. Elliott, A. J. Olszanski, D. C. Altieri, *Cancer Biol Ther.* **2022**, *23*, 117.
- [81] M. F. Mabango, K. S. Wong, M. M. Barghash, E. Leung, S. H. W. Chuang, A. Ardalani, E. M. Majaesic, C. J. Wong, S. Zhang, H. Lang, D. S. Karanewsky, A. A. Iwanowicz, L. M. Graves, E. J. Iwanowicz, A.-C. Gingras, W. A. Houry, *Structure* **2023**, *31*, 185.
- [82] Y. E. Greer, L. Hernandez, E. M. J. Fennell, M. Kundu, D. Voeller, R. Chari, S. F. Gilbert, T. S. K. Gilbert, S. Ratnayake, B. Tang, M. Hafner, Q. Chen, D. Meerzaman, E. Iwanowicz, C. M. Annunziata, L. M. Graves, S. Lipkowitz, *Cancer Res Commun.* **2022**, *2*, 1144.
- [83] Y. Chu, J. Park, E. Kim, S. Lee, *Materials (Basel)* **2021**, *14*, 4180.
- [84] J. Michaelis, S. Bozkurt, J. Schäfer, C. Münch, *Bio Protoc.* **2022**, *12*, e4578.
- [85] Z. Li, T.-B. Ren, X.-X. Zhang, S. Xu, X.-Y. Gong, Y. Yang, G. Ke, L. Yuan, X.-B. Zhang, *Anal Chem.* **2021**, *93*, 2235.
- [86] M. Li, Y. Huang, S. Song, S. Shuang, C. Dong, *ACS Appl. Bio Mater.* **2022**, *5*, 2777.
- [87] X. Luo, C. Zhang, F. Yuan, S. Cheng, Y. Zhu, M. Xiang, X. Hu, Y. Xian, *Anal Chem.* **2022**, *94*, 15790.
- [88] Y. Huang, M. Li, Q. Zan, R. Wang, S. Shuang, C. Dong, *Anal Chem.* **2023**.
- [89] N. Zheng, Q. Wang, S. Zhang, C. Mao, L. He, S. Liu, *J. Mater. Chem. B* **2022**, *10*, 7450.
- [90] W. Chen, K. Shi, B. Chu, X. Wei, Z. Qian, *Nano Lett.* **2019**, *19*, 2905.
- [91] Y. Liu, X. Zhang, M. Zhou, X. Nan, X. Chen, X. Zhang, *ACS Appl. Mater. Interfaces* **2017**, *9*, 43498.
- [92] X. Li, T. Zhang, X. Diao, L. Yu, Y. Su, J. Yang, Z. Shang, S. Liu, J. Zhou, G. Li, H. Chi, *Molecules* **2023**, *28*, 3962.

- [93] G.-G. Yang, Z.-Y. Pan, D.-Y. Zhang, Q. Cao, L.-N. Ji, Z.-W. Mao, *ACS Appl. Mater. Interfaces* **2020**, *12*, 43444.
- [94] C.-L. Kuo, H.-Y. Chou, Y.-C. Chiu, A. N. Cheng, C.-C. Fan, Y.-N. Chang, C.-H. Chen, S. S. Jiang, N.-J. Chen, A. Y.-L. Lee, *Cancer Lett.* **2020**, *474*, 138.
- [95] S. Izawa, K. Kono, K. Mimura, Y. Kawaguchi, M. Watanabe, T. Maruyama, H. Fujii, *Cancer Immunol. Immunother.* **2011**, *60*, 1801.
- [96] L. Yang, N. Li, W. Pan, Z. Yu, B. Tang, *Anal Chem.* **2015**, *87*, 3678.
- [97] Y. Chen, J. Ye, G. Lv, W. Liu, H. Jiang, X. Liu, X. Wang, *Biosensors (Basel)* **2022**, *12*, 111.
- [98] B. Yu, H. Wei, Q. He, C. A. Ferreira, C. J. Kutyreff, D. Ni, Z. T. Rosenkrans, L. Cheng, F. Yu, J. W. Engle, X. Lan, W. Cai, *Angew Chem Int Ed Engl.* **2018**, *57*, 218.
- [99] Y. Tan, X. Yang, S. Dai, K. Lian, L. Wen, Y. Zhu, T. Meng, X. Liu, H. Yuan, F. Hu, *Polym. Chem.* **2019**, *10*, 512.
- [100] T. Jiang, L. Zhou, H. Liu, P. Zhang, G. Liu, P. Gong, C. Li, W. Tan, J. Chen, L. Cai, *Anal Chem.* **2019**, *91*, 6996.
- [101] K. L. Horton, K. M. Stewart, S. B. Fonseca, Q. Guo, S. O. Kelley, *Chem. Biol.* **2008**, *15*, 375.
- [102] S. R. Jean, M. Ahmed, E. K. Lei, S. P. Wisnovsky, S. O. Kelley, *Acc Chem Res.* **2016**, *49*, 1893.
- [103] M. T. Jeena, K. Jeong, E. M. Go, Y. Cho, S. Lee, S. Jin, S.-W. Hwang, J. H. Jang, C. S. Kang, W.-Y. Bang, E. Lee, S. K. Kwak, S. Kim, J.-H. Ryu, *ACS Nano* **2019**, *13*, 11022.
- [104] N. Sun, D. Malide, J. Liu, I. I. Rovira, C. A Combs, T. Finkel, *Nat. Protoc.* **2017**, *12*, 1576.
- [105] K. Liu, X. Li, Z. Li, J. Cao, X. Li, Y. Xu, L. Liu, T. Zhao, *Front Cell Dev Biol.* **2022**, *10*, 910464.
- [106] N. Sun, J. Yun, J. Liu, D. Malide, C. Liu, I. I. Rovira, K. M. Holmström, M. M. Ferguson, Y. H. Yoo, C. A. Combs, T. Finkel, *Mol. Cell.* **2015**, *60*, 685.
- [107] Z. Yuan, M. Xu, T. Wu, X. Zhang, Y. Shen, U. Ernest, L. Gui, F. Wang, Q. He, H. Chen, *Talanta* **2019**, *198*, 323.
- [108] B.-Z. Wang, Y.-C. Zhou, Y.-W. Lin, X.-C. Chen, Z.-Y. Yu, Y.-H. Xu, J.-H. Tan, Z.-S. Huang, S.-B. Chen, *Molecules* **2023**, *28*, 2690.
- [109] X. Guo, N. Yang, W. Ji, H. Zhang, X. Dong, Z. Zhou, L. Li, H.-M. Shen, S. Q. Yao, W. Huang, *Adv. Mater.* **2021**, *33*, 2007778.
- [110] H. Crawford, M. Dimitriadi, J. Bassin, M. T. Cook, T. F. Abelha, J. Calvo-Castro, *Chemistry* **2022**, *28*, 202202366.
- [111] A. Wongrakpanich, S. M. Geary, M.-L. A. Joiner, M. E. Anderson, A. K. Salem, *Nanomedicine* **2014**, *9*, 2531.
- [112] R. K. Pathak, N. Kolishetti, S. Dhar, *Wiley Interdiscip Rev Nanomed Nanobiotechnol* **2015**, *7*, 315.
- [113] K. S. Allemailem, A. Almatroudi, M. A. Alsahl, A. Aljaghwani, A. M. El-Kady, A. H. Rahmani, A. A. Khan, *Int J Nanomedicine* **2021**, *16*, 3907.
- [114] D. W. Deamer, *FASEB J.* **2010**, *24*, 1308.
- [115] Y. (C.) Barenholz, *J Control Release* **2012**, *160*, 117.
- [116] X. Cheng, D. Feng, J. Lv, X. Cui, Y. Wang, Q. Wang, L. Zhang, *Cancers (Basel)* **2023**, *15*, 666.
- [117] J. Zhang, X. Sun, L. Wang, Y. K. Wong, Y. M. Lee, C. Zhou, G. Wu, T. Zhao, L. Yang, L. Lu, J. Zhong, D. Huang, J. Wang, *Redox Biol.* **2018**, *19*, 263.
- [118] F. Zhao, O. Vakhrusheva, S. D. Markowitsch, K. S. Slade, I. Tsaur, J. Cinatl, M. Michaelis, T. Efferth, A. Haferkamp, E. Juengel, *Cells* **2020**, *9*, 2643.
- [119] L. Gu, J. Zhang, D. Liu, J. Chen, S. Liu, Q. Peng, Y. Tian, M. Du, J. Zhang, W. Xiao, S. Shen, J. Wang, *J Nanobiotechnology* **2022**, *20*, 376.
- [120] N. A. D'angelo, M. A. Noronha, M. C. C. Câmara, I. S. Kurnik, C. Feng, V. H. S. Araujo, J. H. P. M. Santos, V. Feitosa, J. V. D. Molino, C. O. Rangel-Yagui, M. Chorilli, E. A. Ho, A. M. Lopes, *Biomater Adv* **2022**, *133*, 112623.
- [121] H. Chen, Z. Fang, M. Song, K. Liu, *Eur J Med Chem.* **2022**, *241*, 114648.
- [122] Y. Xu, Y. Yao, L. Wang, H. Chen, N. Tan, *Int J Nanomedicine* **2021**, *16*, 4929.
- [123] H. Morita, T. Yamamiya, K. Takeya, H. Itokawa, *Chem Pharm Bull (Tokyo)* **1992**, *40*, 1352.
- [124] Y. Wang, D. Guo, J. He, L. Song, H. Chen, Z. Zhang, N. Tan, *Biochem Biophys Res Commun.* **2019**, *512*, 819.
- [125] I. R. Calori, H. Bi, A. C. Tedesco, *ACS Appl. Bio Mater.* **2021**, *4*, 195.
- [126] H. Chen, C. He, T. Chen, X. Xue, *Biomater Sci.* **2020**, *8*, 3994.
- [127] M. Tian, W. Chen, Y. Wu, J. An, G. Hong, M. Chen, F. Song, W.-H. Zheng, X. Peng, *ACS Appl. Mater. Interfaces* **2022**, *14*, 12050.
- [128] U. Kafle, S. Agrawal, A. K. Dash, *Pharmaceutics* **2022**, *14*, 2783.
- [129] K. Lin, Z. Ma, J. Li, et al., *Adv. Funct. Mater* **2020**, 2008460.
- [130] M. Tang, K. Lin, M. Ramachandran, L. Li, H. Zou, H. Zheng, Z. Ma, Y. Li, *Acta Pharm. Sin. B* **2022**, *12*, 2672.
- [131] J. Ren, J. Zhou, H. Liu, X. Jiao, Y. Cao, Z. Xu, Y. Kang, P. Xue, *Theranostics* **2021**, *11*, 9470.
- [132] J. K. Patra, G. Das, L. F. Fraceto, E. V. R. Campos, M. D. P. Rodriguez-Torres, L. S. Acosta-Torres, L. A. Diaz-Torres, R. Grillo, M. K. Swamy, S. Sharma, S. Habtemariam, H.-S. Shin, *J Nanobiotechnology* **2018**, *16*, 71.
- [133] M.-C. Daniel, D. Astruc, *Chem Rev.* **2004**, *104*, 293.
- [134] S. Buchke, M. Sharma, A. Bora, M. Relekar, P. Bhanu, J. Kumar, *Life (Basel)* **2022**, *12*, 657.
- [135] H. Y. Nukaly, S. A. Ansari, *Cureus* **2023**, *15*, e37803.
- [136] Z.-J. Guan, J.-J. Li, F. Hu, Q.-M. Wang, *Angew Chem Int Ed Engl.* **2022**, *61*, e202209725.
- [137] Y. Genji Srinivasulu, Q. Yao, N. Goswami, J. Xie, *Mater Horiz.* **2020**, *7*, 2596.
- [138] Y. Hua, Z.-H. Shao, A. Zhai, L.-J. Zhang, Z.-Y. Wang, G. Zhao, F. Xie, J.-Q. Liu, X. Zhao, X. Chen, S.-Q. Zang, *ACS Nano* **2023**, *17*, 7837.
- [139] E. Porret, X. Le Guével, J.-L. Coll, *J. Mater. Chem. B* **2020**, *8*, 2216.
- [140] G. Zuber, E. Weiss, M. Chiper, *Nanotechnology* **2019**, *30*, 352001.
- [141] H. Xiong, J. Ye, M. Wang, Y. Wang, X. Liu, H. Jiang, X. Wang, *Biosens. Bioelectron.* **2022**, *218*, 114763.
- [142] X. Yan, S. Li, H. Yan, C. Yu, F. Liu, *Int J Nanomedicine* **2023**, *18*, 1741.
- [143] L. Wu, C. Wang, Y. Li, *Nanomedicine (Lond)* **2022**, *17*, 1567.
- [144] B. Chen, W. Wu, X. Wang, *Curr. Cancer Drug Targets* **2011**, *11*, 184.
- [145] A. Sood, A. Dev, M. N. Sardoiwala, S. R. Choudhury, S. Chaturvedi, A. K. Mishra, S. Karmakar, *Mater Sci Eng C Mater Biol Appl.* **2021**, *129*, 112394.
- [146] M. Moharramenejad, R. E. Malekshah, A. Ehsani, S. Gharanli, M. Shahi, S. A. Alvan, Z. Salariyeh, M. N. Azadani, J. Haribabu, Z. S. Basmenj, A. Khaleghian, H. Saremi, Z. Hassani, E. Momeni, *Adv Colloid Interface Sci.* **2023**, *316*, 102908.
- [147] Y. Deng, Y. Wang, X. Xiao, B. J. Saucedo, Z. Zhu, M. Xie, X. Xu, K. Yao, Y. Zhai, Z. Zhang, J. Chen, *Small* **2022**, *18*, 2202928.
- [148] W. Li, M. Dong, Y. Li, H. Dong, *Adv. Healthcare Mater.* **2023**, 2202986.
- [149] H. Zhou, C. Fu, X. Chen, L. Tan, J. Yu, Q. Wu, L. Su, Z. Huang, F. Cao, X. Ren, J. Ren, P. Liang, X. Meng, *Biomater Sci.* **2018**, *6*, 1535.
- [150] K. Ni, G. Lan, S. S. Veroneau, X. Duan, Y. Song, W. Lin, *Nat Commun.* **2018**, *9*, 4321.
- [151] X. Peng, S. Tang, D. Tang, D. Zhou, Y. Li, Q. Chen, F. Wan, H. Lukas, H. Han, X. Zhang, W. Gao, S. Wu, *Sci Adv.* **2023**, *9*, eadh1736.
- [152] Z. Ouyang, Y. Gao, M. Shen, X. Shi, *Mater Today Bio.* **2021**, *10*, 100111.
- [153] C. Ni, Z. Ouyang, G. Li, et al., *Acta Biomater.* **2023**.
- [154] Y. Guo, Y. Fan, Z. Wang, G. Li, M. Zhan, J. Gong, J.-P. Majoral, X. Shi, M. Shen, *Adv. Mater.* **2022**, *34*, 2206861.
- [155] J. Shi, W. Nie, X. Zhao, X. Yang, H. Cheng, T. Zhou, Y. Zhang, K. Zhang, J. Liu, *Adv Mater.* **2022**, *34*, 2201049.
- [156] S. Liang, C. Sun, P. Yang, P. Ma, S. Huang, Z. Cheng, X. Yu, J. Lin, *Biomaterials* **2020**, *240*, 119850.

- [157] L. Tang, Q. Xiao, Y. Mei, S. He, Z. Zhang, R. Wang, W. Wang, *J. Nanobiotechnology* **2021**, *19*, 423.
- [158] F. Zhou, S. Wu, B. Wu, W. R. Chen, D. Xing, *Small* **2011**, *7*, 2727.
- [159] F. Zhou, S. Wu, Y. Yuan, W. R. Chen, D. Xing, *Small* **2012**, *8*, 1543.
- [160] S. L. Yoong, B. S. Wong, Q. L. Zhou, C. F. Chin, J. Li, T. Venkatesan, H. K. Ho, V. Yu, W. H. Ang, G. Pastorin, *Biomaterials* **2014**, *35*, 748.
- [161] R. Rani, P. Malik, S. Dhania, T. K. Mukherjee, *Pharmaceutics* **2023**, *15*, 227.
- [162] D. Tarn, C. E. Ashley, M. Xue, E. C. Carnes, J. I. Zink, C. J. Brinker, *Acc. Chem. Res.* **2013**, *46*, 792.
- [163] H. Lee, M. Choi, H.-E. Kim, M. Jin, W.-J. Jeon, M. Jung, H. Yoo, J.-H. Won, Y.-G. Na, J.-Y. Lee, H. Seong, H.-K. Lee, C.-W. Cho, *J Control Release* **2022**, *349*, 241.
- [164] P. Dong, J. Hu, S. Yu, Y. Zhou, T. Shi, Y. Zhao, X. Wang, X. Liu, *Small Methods* **2021**, *5*, e2100581.
- [165] S. Naz, M. Wang, Y. Han, B. Hu, L. Teng, J. Zhou, H. Zhang, J. Chen, *Int J Nanomedicine* **2019**, *14*, 2533.
- [166] F. Yuan, S. Li, Z. Fan, X. Meng, L. Fan, S. Yang, *Nano Today* **2016**, *11*, 565.
- [167] L. Tian, H. Ji, W. Wang, X. Han, X. Zhang, X. Li, L. Guo, L. Huang, W. Gao, *Bioorg. Chem.* **2023**, *130*, 106259.
- [168] Kirbas Cilingir E, E. S. Seven, Y. Zhou, et al., *J. Colloid Interface Sci.* **2021**, *592*, 485.
- [169] G. Qi, Y. Zhang, S. Xu, C. Li, D. Wang, H. Li, Y. Jin, *Anal. Chem.* **2018**, *90*, 13356.
- [170] R. Kotha, D. D. Kara, R. Roychowdhury, K. Tanvi, M. Rathnanand, *Adv. Pharm. Bull.* **2023**, *13*, 218.
- [171] S. Mazumdar, D. Chitkara, A. Mittal, *Acta Pharm. Sin. B* **2021**, *11*, 903.
- [172] S. Yang, B. Sun, F. Liu, N. Li, M. Wang, P. Wu, G.-L. Wu, H. Fang, Y. He, W. Zhou, H. Xiao, X. Tan, L. Tang, S. Zhu, Q. Yang, *Small* **2023**, e2207995.
- [173] F. Yang, W. Yu, Q. Yu, X. Liu, C. Liu, C. Lu, X. Liao, Y. Liu, N. Peng, *Small* **2023**, *19*, e2206124.
- [174] Y. Geng, J. Xiang, S. Shao, J. Tang, Y. Shen, *J Control Release* **2022**, *342*, 122.
- [175] K. Fukasawa, *Cancer Lett.* **2005**, *230*, 6.
- [176] A. C. F. Bolhaqueiro, B. Ponsioen, B. Bakker, S. J. Klaasen, E. Kucukkose, R. H. Van Jaarsveld, J. Vivié, I. Verlaan-Klink, N. Hami, D. C. J. Spierings, N. Sasaki, D. Dutta, S. F. Boj, R. G. J. Vries, P. M. Lansdorp, M. Van De Wetering, A. Van Oudenaarden, H. Clevers, O. Kranenburg, F. Foijer, H. J. G. Snippert, G. J. P. L. Kops, *Nat. Genet.* **2019**, *51*, 824.
- [177] N. Vargas-Rondón, V. Villegas, M. Rondón-Lagos, *Cancers (Basel)* **2017**, *10*, 4.
- [178] S. F. Bakhour, B. Ngo, A. M. Laughney, J.-A. Cavallo, C. J. Murphy, P. Ly, P. Shah, R. K. Sriram, T. B. K. Watkins, N. K. Taunk, M. Duran, C. Pauli, C. Shaw, K. Chadalavada, V. K. Rajasekhar, G. Genovese, S. Venkatesan, N. J. Birkbak, N. Mcgranahan, M. Lundquist, Q. Laplant, J. H. Healey, O. Elemento, C. H. Chung, N. Y. Lee, M. Imielinski, G. Nanjangud, D. Pe'er, D. W. Cleveland, S. N. Powell, et al., *Nature* **2018**, *553*, 467.
- [179] L. F. Flores, B. R. Tader, E. J. Tolosa, A. N. Sigafoos, D. L. Marks, M. E. Fernandez-Zapico, *Cells* **2021**, *10*, 2624.
- [180] E. Heng, S. Thanedar, H. H. Heng, *Genes (Basel)* **2023**, *14*, 493.
- [181] N. Mcgranahan, R. A. Burrell, D. Endesfelder, M. R. Novelli, C. Swanton, *EMBO Rep.* **2012**, *13*, 528.
- [182] J. B. Stevens, S. D. Horne, B. Y. Abdallah, C. J. Ye, H. H. Heng, *Cancer Metastasis Rev.* **2013**, *32*, 391.
- [183] A. A. Asnafi, Z. Deris Zayeri, S. Shahrabi, K. Zibara, T. Vosoughi, *J. Cell. Physiol.* **2019**, *234*, 5798.
- [184] M. Grigorova, J. M. Staines, H. Ozdag, C. Caldas, P. A. W. Edwards, *Cytogenet Genome Res.* **2004**, *104*, 333.
- [185] I. Mármol, C. Sánchez-De-Diego, A. Pradilla Dieste, E. Cerrada, M. Rodriguez Yoldi, *Int. J. Mol. Sci.* **2017**, *18*, 197.
- [186] J. Rohrberg, D. Van De Mark, M. Amouzgar, J. V. Lee, M. Taileb, A. Corella, S. Kilinc, J. Williams, M.-L. Jokisch, R. Camarda, S. Balakrishnan, R. Shankar, A. Zhou, A. N. Chang, B. Chen, H. S. Rugo, S. Dumont, A. Goga, *Cell Rep.* **2020**, *30*, 3368.
- [187] L. A. Donehower, T. Soussi, A. Korkut, Y. Liu, A. Schultz, M. Cardenas, X. Li, O. Babur, T.-K. Hsu, O. Lichtarge, J. N. Weinstein, R. Akbani, D. A. Wheeler, *Cell Rep.* **2019**, *28*, 1370.
- [188] S.-Q. Hou, M. Ouyang, A. Brandmaier, H. Hao, W. H. Shen, *BioEssays* **2017**, *39*, 1700082.
- [189] R. Sotillo, J.-M. Schwartzman, N. D. Socci, R. Ben Ezra, *Nature* **2010**, *464*, 436.
- [190] A. R. Venkitaraman, *DNA Repair (Amst)* **2019**, *81*, 102668.
- [191] A. Cazzola, C. Schlegel, I. Janssen, T. Bochtler, A. Jauch, A. Krämer, *Leukemia* **2019**, *33*, 2619.
- [192] E. M. C. Britigan, J. Wan, D. K. Sam, S. E. Copeland, A. L. Lasek, L. C. F. Hrycyniak, L. Wang, A. Audhya, M. E. Burkard, A. Roopra, B. A. Weaver, *Front Cell Dev Biol.* **2022**, *10*, 1018161.
- [193] A. Boukaba, J. Liu, C. Ward, Q. Wu, A. Arnaoutov, J. Liang, E. M. Pugacheva, M. Dasso, V. Lobanenkov, M. Esteban, A. V. Strunnikov, *Proc Natl Acad Sci U S A* **2022**, *119*, e2204071119.
- [194] K. Pavlakis, I. Messini, T. Vrekoussis, T. Panoskaltsis, D. Chrissanthakis, P. Yiannou, E. N. Stathopoulos, *Gynecol. Oncol.* **2010**, *119*, 516.
- [195] I. Singh, T. P. Lele, *Results Probl Cell Differ.* **2022**, *70*, 443.
- [196] Y. Yao, W. Yang, *Curr Cancer Drug Targets* **2005**, *5*, 595.
- [197] A. R. Elhamamsy, B. J. Metge, H. A. Alsheikh, L. A. Shevde, R. S. Samant, *Cancer Res.* **2022**, *82*, 2344.
- [198] H. Xue, J. Lu, H. Yan, J. Huang, H.-B. Luo, M. S. Wong, Y. Gao, X. Zhang, L. Guo, *Talanta* **2022**, *237*, 122898.
- [199] S. D. Özürk, Ç. Özürk, O. Okcu, B. Şen, R. Bedir, *Turk J Med Sci.* **2022**, *52*, 975.
- [200] C. R. Abdo-Banhos, J. A. Cordeiro, C. S. Rosa, H. E. Bicudo, *J Sub-microsc Cytol Pathol.* **2004**, *36*, 37.
- [201] J. Janczukowicz, *Folia Neuropathol* **2003**, *41*, 97.
- [202] K. Ma, H. Yang, X. Wu, F. Huo, F. Cheng, C. Yin, *Angew Chem Int Ed Engl.* **2023**, *62*, e202301518.
- [203] B. Pang, J. De Jong, X. Qiao, L. F. A. Wessels, J. Neefjes, *Nat. Chem. Biol.* **2015**, *11*, 472.
- [204] J. J. Castro, M. Ribo, A. Benito, M. Vilanova, *Curr. Med. Chem.* **2013**, *20*, 1225.
- [205] F. Tamanoi, K. Yoshikawa, *Enzymes* **2022**, *52*, 11.
- [206] F. Yang, C. J. Kemp, S. Henikoff, *Curr Biol.* **2013**, *23*, 782.
- [207] S. Dasari, P. Bernard Tchounwou, *Eur. J. Pharmacol.* **2014**, *740*, 364.
- [208] R. Yin, S. Gou, X. Liu, L. Lou, J. Inorg. Biochem. **2011**, *105*, 1095.
- [209] T. Makovec, *Radial Oncol.* **2019**, *53*, 148.
- [210] J. S. Baxter, D. Zatreenau, S. J. Pettitt, C. J. Lord, *Mol. Oncol.* **2022**, *16*, 3811.
- [211] P. Jangili, N. Kong, J. H. Kim, J. Zhou, H. Liu, X. Zhang, W. Tao, J. S. Kim, *Angew Chem Int Ed Engl.* **2022**, *61*, e202117075.
- [212] Y. Zhao, Q. Luo, J. Mo, J. Li, D. Ye, Z. Ao, L. Chen, J. Liu, *J Cancer* **2020**, *11*, 3701.
- [213] C. Uhler, G. V. Shivashankar, *Trends Cancer* **2018**, *4*, 320.
- [214] A. Vivante, E. Brozgol, I. Bronshtein, Y. Garini, *Methods* **2017**, *123*, 128.
- [215] H. Chu, X. Han, H. Jiang, F. Li, H. Li, T. Zhao, *Ann. Hematol.* **2011**, *90*, 1299.
- [216] L. Yang, Y. Chen, S. Ling, J. Wang, G. Wang, B. Zhang, H. Zhao, Q. Zhao, J. Mao, *Front Oncol.* **2022**, *12*, 953934.
- [217] N. Iftimia, D. X. Hammer, M. Mujat, V. Deshpande, S. Cizginer, W. Brugge, *Annu Int Conf IEEE Eng Med Biol Soc.* **2009**, *2009*, 4067.
- [218] A. Singh, D. Chaudhary, A. P. Waghchoure, R. N. Kalariya, R. S. Bhosale, *Prog Mol Biol Transl Sci.* **2021**, *184*, 205.

- [219] J. Wu, Q. Hu, Q. Chen, J. Dai, X. Wu, S. Wang, X. Lou, F. Xia, *ACS Appl. Bio Mater.* **2020**, *3*, 9002.
- [220] Z. Lei, L. Ding, C. Yao, F. Mo, C. Li, Y. Huang, X. Yin, M. Li, J. Liu, Y. Zhang, C. Ling, Y. Wang, *Adv. Mater.* **2019**, *31*, 1807456.
- [221] A. N. Guterres, J. Villanueva, *Oncogene* **2020**, *39*, 5811.
- [222] W. Liu, Z. Fan, L. Li, M. Li, *ChemBioChem* **2022**, *23*, e202200307.
- [223] G. Yang, Q. Zhang, L. Ma, Y. Zheng, F. Tian, H. Li, P. Zhang, L.-L. Qu, *Anal. Chim. Acta* **2020**, *1098*, 133.
- [224] N. Groysbeck, V. Hanss, M. Donzeau, J.-M. Strub, S. Cianfrani, D. Spehner, M. Bahri, O. Ersen, M. Eltsov, P. Schultz, G. Zuber, *Small Methods* **2023**, *7*, e2300098.
- [225] L. Pan, J. Liu, J. Shi, *Chem. Soc. Rev.* **2018**, *47*, 6930.
- [226] S. N. Tammam, H. M. E. Azzazy, A. Lamprecht, *J Control Release* **2016**, *229*, 140.
- [227] D. Zink, A. H. Fischer, J. A. Nickerson, *Nat. Rev. Cancer* **2004**, *4*, 677.
- [228] A. Pogorzelska, M. Mazur, M. Świtalska, J. Wietrzyk, D. Sigorski, K. Fronczyk, K. Wiktorska, *Biomed. Pharmacother* **2023**, *161*, 114490.
- [229] A. Akewar, N. Mahajan, R. Kharwade, P. Gangane, *Curr Drug Deliv.* **2023**, *20*, 350.
- [230] Y. Wang, Y. Tang, X.-M. Zhao, G. Huang, J.-H. Gong, S.-D. Yang, H. Li, W.-J. Wan, C.-H. Jia, G. Chen, X.-N. Zhang, *Acta Biomater.* **2022**, *153*, 481.
- [231] F. Darabi, M. Saidijam, F. Nouri, R. Mahjub, M. Soleimani, *Biomed. Res. Int.* **2022**, *2022*, 6253978.
- [232] C. Seraya-Bareket, A. Weisz, E. Shinderman-Maman, S. Teper-Roth, D. Stamler, N. Arbib, Y. Kadan, A. Fishman, D. Kidron, E. Edelstein, M. Ellis, O. Ashur-Fabian, *Oncogenesis* **2020**, *9*, 69.
- [233] A. Weisz, U. Abadi, L. Mausbach, D. Gurwitz, M. Ellis, O. Ashur-Fabian, *Hematol Oncol.* **2022**, *40*, 73.
- [234] L. Zhang, X. Shan, X. Meng, T. Gu, Q. Lu, J. Zhang, J. Chen, Q. Jiang, X. Ning, *Biomaterials* **2019**, *223*, 119471.
- [235] T. I. Shabatina, O. I. Vernaya, N. L. Shimanovskiy, M. Y. Melnikov, *Pharmaceutics* **2023**, *15*, 1181.
- [236] C. Xu, J. Xie, N. Kohler, E. G. Walsh, Y. E. Chin, S. Sun, *Chem Asian J.* **2008**, *3*, 548.
- [237] X. Wang, J. Zhou, B. Chen, Z. Tang, J. Zhang, L. Li, J. Tang, *J. Nanosci. Nanotechnol.* **2016**, *16*, 6560.
- [238] A. Farzin, S. A. Etesami, J. Quint, A. Memic, A. Tamayol, *Adv. Healthcare Mater.* **2020**, *9*, 1901058.
- [239] H. Peng, J. Tang, R. Zheng, G. Guo, A. Dong, Y. Wang, W. Yang, *Adv. Healthcare Mater.* **2017**, *6*, 1601289.
- [240] S. Özçelik, G. Pratz, *Nanotechnology* **2020**, *31*, 415102.
- [241] L. Xie, C. Zhang, M. Liu, J. Huang, X. Jin, C. Zhu, M. Lv, N. Yang, S. Chen, M. Shao, X. Du, G. Feng, *ACS Appl. Mater. Interfaces* **2023**, *15*, 10541.
- [242] R. Qi, Y. Gao, Y. Tang, R.-R. He, T.-L. Liu, Y. He, S. Sun, B.-Y. Li, Y.-B. Li, G. Liu, *AAPS J.* **2009**, *11*, 395.
- [243] A. Chauhan, *Molecules* **2018**, *23*, 938.
- [244] Y. Lu, S. Han, H. Zheng, R. Ma, Y. Ping, J. Zou, H. Tang, Y. Zhang, X. Xu, F. Li, *Int J Nanomedicine* **2018**, *13*, 5937.
- [245] P. Ma, H. Yu, X. Zhang, H. Mu, Y. Chu, L. Ni, P. Xing, Y. Wang, K. Sun, *Pharm. Res.* **2017**, *34*, 121.
- [246] Z. Zhao, S. Lou, Y. Hu, J. Zhu, C. Zhang, *Mol Pharm.* **2017**, *14*, 2697.
- [247] R. Jha, A. Singh, P. K. Sharma, N. K. Fuloria, *J Drug Deliv Sci Technol.* **2020**, *58*, 101811.
- [248] T. Saliev, *CJ Carbon Res.* **2019**, *5*, 29.
- [249] M. Sheikhpour, M. Naghinejad, A. Kasaeian, A. Lohrasbi, S. S. Shahraeini, S. Zomorodbakhsh, *Int J Nanomedicine* **2020**, *15*, 7063.
- [250] W. Wijagkanalan, *Front Biosci (Landmark Ed)* **2011**, *16*, 2970.
- [251] Y.-J. Lu, K.-C. Wei, C.-C. M. Ma, S.-Y. Yang, J.-P. Chen, *Colloids Surf B Biointerfaces* **2012**, *89*, 1.
- [252] A. Adam, D. Mertz, *Nanomaterials* **2023**, *13*, 1342.
- [253] Y. Zhuo, X. Huang, N. L. Lin, et al., *Biomater. Sci.* **2023**.
- [254] W. Du, S. Du, X. Dong, H. Bai, J. Jiang, S. Hao, F. Yang, Q. Xiao, B. Zhang, J. Ge, L. Gao, L. Li, S. Q. Yao, W. Huang, *Biomaterials* **2023**, *294*, 122000.
- [255] Y. Ma, G. Mao, G. Wu, Z. Cui, X.-E. Zhang, W. Huang, *ACS Appl. Mater. Interfaces* **2021**, *13*, 7890.
- [256] K. Naik, S. Chaudhary, L. Ye, A. S. Parmar, *Front Bioeng Biotechnol.* **2022**, *10*, 882100.
- [257] V. Manikandan, N. Y. Lee, *Environ. Res.* **2022**, *212*, 113283.
- [258] P. T. M. Phuong, H. J. Won, A. I. Robby, S. G. Kim, G.-B. Im, S. H. Bhang, G. Lee, S. Y. Park, *ACS Appl. Mater. Interfaces* **2020**, *12*, 37929.
- [259] B. Wu, K. Li, F. Sun, J. Niu, R. Zhu, Y. Qian, S. Wang, *Adv. Healthcare Mater.* **2021**, *10*, e2100512.
- [260] Y.-S. Lin, Y. Chen, Y.-H. Tsai, S.-H. Tseng, K.-S. Lin, *J Pediatr Surg.* **2021**, *56*, 1227.
- [261] C. Yu, Z. Long, Q. Qiu, F. Liu, Y. Xu, T. Zhang, R. Guo, W. Zhong, S. Huang, S. Chen, *Bioeng. Transl. Med.* **2021**, *7*, e10270.
- [262] J. Chen, F. Li, J. Gu, X. Zhang, M. Bartoli, J. B. Domenga, Y. Zhou, W. Zhang, V. Paulino, B. C. L. B. Ferreira, N. Michael Brejcha, L. Luo, C. Arduino, F. Verde, F. Zhang, F. Zhang, A. Tagliaferro, J.-H. Olivier, Y. Zhang, R. M. Leblanc, J. *Colloid Interface Sci.* **2023**, *637*, 193.
- [263] J. Wei, D. Fang, *Int. J. Mol. Sci.* **2021**, *22*, 1799.
- [264] J. R. Cubillos-Ruiz, S. E. Bettigole, L. H. Glimcher, *Cell.* **2017**, *168*, 692.
- [265] C. Hetz, K. Zhang, R. J. Kaufman, *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 421.
- [266] E. Madden, S. E. Logue, S. J. Healy, S. Manie, A. Samali, *Biol. Cell.* **2019**, *111*, 1.
- [267] C. M. De La Calle, K. Shee, H. Yang, P. E. Lonergan, H. G. Nguyen, *Nat Rev Urol.* **2022**, *19*, 708.
- [268] G. Bustos, P. Cruz, A. Lovy, C. Cárdenas, *Front Oncol.* **2017**, *7*, 199.
- [269] C. Bosc, N. Broin, M. Fanjul, E. Saland, T. Farge, C. Courdy, A. Batut, R. Masoud, C. Larrue, S. Skuli, N. Espagnolle, J.-C. Pagès, A. Carrier, F. Bost, J. Bertrand-Michel, J. Tamburini, C. Récher, S. Bertoli, V. Mansat-De Mas, S. Manenti, J.-E. Sarry, C. Joffre, *Nat. Commun.* **2020**, *11*, 4056.
- [270] A. Khatib, B. Solairmuthu, M. Ben Yosef, A. Abu Rmaileh, M. Tanna, G. Oren, M. Schlesinger Frisch, J. H. Axelrod, M. Lichtenstein, Y. D. Shaul, *Proc Natl Acad Sci U S A.* **2020**, *117*, 21420.
- [271] Y. Jin, Y. Han, S. Yang, J. Cao, M. Jiang, J. Liang, *Cell Prolif.* **2022**, *55*, e13253.
- [272] L. Han, J. Shi, L. Zhao, J. Deng, Y. Li, H. Zhao, H. Wang, Y. Yan, F. Zou, *Exp. Cell Res.* **2022**, *418*, 113265.
- [273] C. B. Nava Lauson, S. Tiberti, et al., *Cell Metab.* **2023**.
- [274] J. Wang, D. Jiang, Z. Li, S. Yang, J. Zhou, G. Zhang, Z. Zhang, Y. Sun, Z. Zhang, X. Li, L. Tao, J. Shi, Y. Lu, L. Zheng, C. Song, K. Yang, *Sci. Rep.* **2020**, *10*, 4025.
- [275] Z. Tu, Q. Ouyang, X. Long, L. Wu, J. Li, X. Zhu, K. Huang, *Front Immunol.* **2022**, *13*, 837512.
- [276] M. Tian, Y. Ma, W. Lin, *Acc. Chem. Res.* **2019**, *52*, 2147.
- [277] M. Wagner, M. Sobczyński, M. Jasek, K. Pawełczyk, I. Porębska, P. Kuśnierzyc, A. Wiśniewski, *BMC Cancer* **2023**, *23*, 383.
- [278] D. Kourmantou, E. Barnea, A. Martin-Esteban, Z. Maben, A. Papakyriakou, A. Mpakali, P. Kokkala, H. Pratsinis, D. Georgiadis, L. J. Stern, A. Admon, E. Stratikos, *Cancer Immunol. Immunother.* **2019**, *68*, 1245.
- [279] S. Xu, H.-W. Liu, X.-X. Hu, S.-Y. Huan, J. Zhang, Y.-C. Liu, L. Yuan, F.-L. Qu, X.-B. Zhang, W. Tan, *Anal Chem.* **2017**, *89*, 7641.
- [280] Z. Li, Z. Li, *Biochim Biophys Acta* **2012**, *1826*, 13.
- [281] H. Zhao, H. Meng, J. Wen, C. Wang, J. Liu, G. Huang, *Mol Imaging Biol.* **2020**, *22*, 772.
- [282] K. Paydar, S. M. Seraj, M. Z. Zadeh, S. Emamzadehfard, S. P. Shamchi, S. Gholami, T. J. Werner, A. Alavi, *Mol Imaging Biol.* **2019**, *21*, 1.

- [283] J. Ferda, E. Ferdová, M. Vítovc, D. Glanc, H. Mírka, *Eur J Radiol.* **2022**, *154*, 110458.
- [284] Ferdinandus, J. R. Tan, J. H. Lim, S. Arai, K. Sou, C.-L. K. Lee, *Analyst.* **2022**, *147*, 3570.
- [285] X. Chen, Z. Zhang, W. Luo, Z. Zhuang, Z. Zhao, L. Wang, D. Wang, B. Z. Tang, *Biomaterials* **2022**, *287*, 121680.
- [286] Y. Zhao, H. Li, Z. Chai, W. Shi, X. Li, H. Ma, *Chem Commun (Camb)* **2020**, *56*, 6344.
- [287] C. Xiang, J. Xiang, X. Yang, B. Zhu, Q. Mo, L. Zhou, P. Gong, *Analyst* **2022**, *147*, 789.
- [288] X. Yue, J. Chen, W. Chen, B. Wang, H. Zhang, X. Song, *Spectrochim Acta A Mol Biomol Spectrosc.* **2021**, *250*, 119347.
- [289] L. Zhou, Y. Li, A. Zhou, G. Zhang, Z.-Q. Cheng, Y.-X. Ge, S.-K. Liu, R. B. Azevedo, J. Zhang, S. Jiang, C.-S. Jiang, *J Fluoresc.* **2020**, *30*, 1357.
- [290] L. Zhou, Z.-Q. Cheng, N. Li, Y.-X. Ge, H.-X. Xie, K. Zhu, A. Zhou, J. Zhang, K.-M. Wang, C.-S. Jiang, *Spectrochim Acta A Mol Biomol Spectrosc.* **2020**, *240*, 118578.
- [291] X. Tian, T. Liu, M. Zhu, J. Peng, J. Cui, L. Feng, X. Huo, J. Yuan, X. Ma, *Anal. Chem.* **2022**, *94*, 9572.
- [292] L. Fang, G. Trigiante, R. Crespo-Otero, C. S. Hawes, M. P. Philpott, C. R. Jones, M. Watkinson, *Chem. Sci.* **2019**, *10*, 10881.
- [293] M. Yang, J. Fan, J. Zhang, J. Du, X. Peng, *Chem. Sci.* **2018**, *9*, 6758.
- [294] A. H. Mehmood, B. Dong, Y. Lu, W. Song, Y. Sun, W. Lin, *Anal. Methods* **2021**, *13*, 2204.
- [295] X. Tian, F. Yan, J. Zheng, X. Cui, L. Feng, S. Li, L. Jin, T. D. James, X. Ma, *Anal. Chem.* **2019**, *91*, 15840.
- [296] Y. Tang, Y. Ma, A. Xu, G. Xu, W. Lin, *Methods Appl Fluoresc.* **2017**, *5*, 024005.
- [297] S. P. Aryal, M. Xia, E. Adindu, C. Davis, P. I. Ortinski, C. I. Richards, *Anal. Chem.* **2022**, *94*, 2099.
- [298] A. Giuffrè, C. S. Tomé, D. G. F. Fernandes, K. Zuhra, J. B. Vicente, *Adv. Exp. Med. Biol.* **2020**, *1219*, 335.
- [299] Y. S. Kafuti, S. Zeng, X. Liu, J. Han, M. Qian, Q. Chen, J. Wang, X. Peng, J. Yoon, H. Li, *Chem Commun (Camb)* **2023**, *59*, 2493.
- [300] L. Bettaiel, M. Brulé, A. Chomy, M. Diedro, M. Fruit, E. Happernegg, L. Heni, A. Horochowska, M. Housseini, K. Klouyovo, A. Laratte, A. Leroy, P. Lewandowski, J. Louvieux, A. Moitié, R. Tellier, S. Titah, D. Vanauberg, F. Woesteland, N. Prevarskaia, V. Y. Lehen'kyi, *Cancers (Basel)* **2021**, *13*, 3085.
- [301] S. Zheng, X. Wang, D. Zhao, H. Liu, Y. Hu, *Trends Cell Biol.* **2023**, *33*, 312.
- [302] H. Ivanova, M. Kerkhofs, R. M. La Rovere, G. Bultynck, *Front Oncol.* **2017**, *7*, 70.
- [303] C. J. Stefan, *Curr. Opin. Cell Biol.* **2020**, *63*, 125.
- [304] H. Wang, K. Mi, *Front Oncol.* **2023**, *13*, 1110881.
- [305] J. Çoku, D. M. Booth, J. Skoda, M. C. Pedrotty, J. Vogel, K. Liu, A. Vu, E. L. Carpenter, J. C. Ye, M. A. Chen, P. Dunbar, E. Scadden, T. D. Yun, E. Nakamaru-Ogiso, E. Area-Gomez, Y. Li, K. C. Goldsmith, C. P. Reynolds, G. Hajnoczky, M. D. Hogarty, *EMBO J.* **2022**, *41*, 108272.
- [306] M. Benvenuto, V. Angiolini, C. Focaccetti, D. Nardozi, C. Palumbo, R. Carrano, A. Rufini, R. Bei, M. T. Miele, P. Mancini, G. Barillari, M. Cirone, E. Ferretti, G. R. Tundo, L. Mutti, L. Masuelli, R. Bei, *Biol. Direct.* **2023**, *18*, 17.
- [307] N. Naradun, K. Talabnín, K. I. N. Ayuttha, C. Talabnín, *Naunyn Schmiedebergs Arch Pharmacol.* **2023**, *396*, 109.
- [308] X. Li, M. Liang, J. Jiang, R. He, M. Wang, X. Guo, M. Shen, R. Qin, *Int J Biol Sci.* **2018**, *14*, 1291.
- [309] D. M. Lee, M. J. Seo, H. J. Lee, H. J. Jin, K. S. Choi, *Biochem. Biophys. Res. Commun.* **2022**, *596*, 56.
- [310] Z. Yao, X. Zhang, F. Zhao, S. Wang, A. Chen, B. Huang, J. Wang, X. Li, *ACS Chem. Neurosci.* **2020**, *11*, 1337.
- [311] C. Salvagno, J. K. Mandula, P. C. Rodriguez, J. R. Cubillos-Ruiz, *Trends Cancer* **2022**, *8*, 930.
- [312] Q. Wang, H. Mora-Jensen, M. A. Weniger, P. Perez-Galan, C. Wolford, T. Hai, D. Ron, W. Chen, W. Trenkle, A. Wiestner, Y. Ye, *Proc Natl Acad Sci U S A.* **2009**, *106*, 2200.
- [313] S. J. Marciak, J. E. Chambers, D. Ron, *Nat Rev Drug Discov.* **2022**, *21*, 115.
- [314] Y. Erzurumlu, E. Aydogdu, H. K. Dogan, D. Catakli, M. T. Muhammed, B. Buyukasdic, *Cell Signal.* **2023**, *103*, 110577.
- [315] L. Wu, D. Zhang, L. Zhou, Y. Pei, Y. Zhuang, W. Cui, J. Chen, *EBioMedicine* **2019**, *41*, 384.
- [316] C. Wang, X. Dai, S. Wu, W. Xu, P. Song, K. Huang, *Nat. Commun.* **2021**, *12*, 2616.
- [317] J. Li, F. Qi, H. Su, C. Zhang, Q. Zhang, Y. Chen, P. Chen, L. Su, Y. Chen, Y. Yang, Z. Chen, S. Zhang, *Int J Biol Sci.* **2022**, *18*, 2914.
- [318] M. R. Patel, S. D. Kozuch, C. N. Cultrara, R. Yadav, S. Huang, U. Samuni, J. Koren, G. Chiosis, D. Sabatino, *Nano Lett.* **2016**, *16*, 6099.
- [319] R. K. Singla, P. Sharma, D. Kumar, R. K. Gautam, R. Goyal, C. Tsagkaris, A. K. Dubey, H. Bansal, R. Sharma, B. Shen, *Front Pharmacol.* **2022**, *13*, 987088.
- [320] Y. Zhang, X. Feng, X. Jia, J. Zhao, Y. Hao, H. Wang, R. Chen, S. Wang, S. Du, Q. Feng, X. Zhang, *J Drug Target* **2021**, *29*, 1094.
- [321] Y. Yoneda, S. C. J. Steiniger, K. Čapková, J. M. Mee, Y. Liu, G. F. Kaufmann, K. D. Janda, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1632.
- [322] A. A. Elfiky, I. M. Ibrahim, *J. Biomol. Struct. Dyn.* **2021**, *39*, 5248.
- [323] M. Hasani, S. Jafari, H. Akbari Javar, H. Abdollahi, H. Rashidzadeh, *ACS Appl. Bio Mater.* **2023**, *6*, 1019.
- [324] S. Xu, P. Zhang, I. Heing-Becker, J. Zhang, P. Tang, R. Bej, S. Bhatia, Y. Zhong, R. Haag, *Biomaterials* **2022**, *290*, 121844.
- [325] B. Cai, M. Hou, S. Zhang, Z. Xin, J. Huang, J. Yang, Y. Wang, X. Cai, S. Xie, C. Zhang, Y. Huang, *Int J Nanomedicine* **2021**, *16*, 5193.
- [326] B. Tancini, S. Buratta, F. Delo, K. Sagini, E. Chiaradia, R. M. Pellegrino, C. Emiliani, L. Urbanelli, *Membranes (Basel)* **2020**, *10*, 406.
- [327] B. Jiang, X. Zhao, W. Chen, W. Diao, M. Ding, H. Qin, B. Li, W. Cao, W. Chen, Y. Fu, K. He, J. Gao, M. Chen, T. Lin, Y. Deng, C. Yan, H. Guo, *Nat. Commun.* **2022**, *13*, 4141.
- [328] M.-C. Lai, C.-M. Chang, H. S. Sun, *PLoS One* **2016**, *11*, e0153627.
- [329] T. Chao, H.-T. Shih, S.-C. Hsu, P.-J. Chen, Y.-S. Fan, Y.-M. Jeng, Z.-Q. Shen, T.-F. Tsai, Z.-F. Chang, *Autophagy* **2021**, *17*, 3444.
- [330] B. Chazotte, *Cold Spring Harb Protoc.* **2011**, *2011*, pdb.prot5571.
- [331] S. Chikte, N. Panchal, G. Warnes, *Cytometry A* **2014**, *85*, 169.
- [332] F. Kazmi, T. Hensley, C. Pope, R. S. Funk, G. J. Loewen, D. B. Buckley, A. Parkinson, *Drug Metab. Dispos.* **2013**, *41*, 897.
- [333] R. C. R. Gonçalves, E. Belmonte-Reche, J. Pina, M. Costa Da Silva, S. C. S. Pinto, J. Gallo, S. P. G. Costa, M. M. M. Raposo, *Molecules* **2022**, *27*, 8065.
- [334] P. Kaur, K. Singh, *J. Mater. Chem. C* **2019**, *7*, 11361.
- [335] X. Kong, L. Di, Y. Fan, Z. Zhou, X. Feng, L. Gai, J. Tian, H. Lu, *Chem Commun (Camb)* **2019**, *55*, 11567.
- [336] S. Xia, M. Fang, J. Wang, J. Bi, W. Mazi, Y. Zhang, R. L. Luck, H. Liu, *Sens Actuators B Chem.* **2019**, *294*, 1.
- [337] J. Yue, Y. Tao, J. Zhang, H. Wang, N. Wang, W. Zhao, *Chem Asian J.* **2021**, *16*, 850.
- [338] Z. Yu, J. Zhou, X. Dong, W. Zhao, Z. Chen, *Anal. Chim. Acta* **2019**, *1067*, 88.
- [339] C. Xu, Y. Qian, *J. Mater. Chem. B* **2019**, *7*, 2714.
- [340] W.-J. Shi, R. Chen, J. Yang, Y.-F. Wei, Y. Guo, Z.-Z. Wang, J.-W. Yan, L. Niu, *Anal. Chem.* **2022**, *94*, 14707.
- [341] M. Hölttä-Vuori, E. Sezgin, C. Eggeling, E. Ikonen, *Traffic* **2016**, *17*, 1054.
- [342] W. Xu, P. Wu, X. Li, S. Liu, L. Feng, H. Xiong, *Talanta* **2021**, *233*, 122601.
- [343] S. Yao, H.-Y. Ahn, X. Wang, J. Fu, E. W. Van Stryland, D. J. Hagan, K. D. Belfield, *J. Org. Chem.* **2010**, *75*, 3965.

- [344] J. Králová, M. Jurášek, L. Mikšátková, A. Marešová, J. Fähnrich, P. Cihlářová, P. Drašar, P. Bartůněk, V. Král, *Sci. Rep.* **2020**, *10*, 22053.
- [345] F. Wang, S. Yu, Z. Xu, L. Li, Y. Dang, X. Xu, Y. Luo, Z. Cheng, H. Yu, W. Zhang, A. Zhang, C. Ding, *Anal. Chem.* **2018**, *90*, 7953.
- [346] N. Fan, P. Li, Y. Zhou, C. Wu, X. Wang, Z. Liu, B. Tang, *ACS Sens.* **2022**, *7*, 71.
- [347] Q. Zong, R. Zheng, X. Xiao, M. Jiang, J. Li, Y. Yuan, *J Control Release* **2021**, *338*, 307.
- [348] X. Wei, J. Li, X. Yang, B. Dong, B. Geng, Z. Li, X. Hu, B. Ding, J. Zhang, M. Yan, *Anal. Chim. Acta* **2022**, *1192*, 339354.
- [349] Y. Tang, Y. Zhao, W. Lin, *Nat. Protoc.* **2020**, *15*, 3499.
- [350] X. Li, Y. Pan, H. Chen, Y. Duan, S. Zhou, W. Wu, S. Wang, B. Liu, *Anal. Chem.* **2020**, *92*, 5772.
- [351] Q. Jia, R. Zhang, Y. Wang, H. Yan, Z. Li, Y. Feng, Y. Ji, Z. Yang, Y. Yang, K. Pu, Z. Wang, *Sci Bull (Beijing)* **2022**, *67*, 288.
- [352] A. Ballabio, J. S. Bonifacino, *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 101.
- [353] T. D. Cong, Z. Wang, M. Hu, Q. Han, B. Xing, *ACS Nano* **2020**, *14*, 5836.
- [354] Y. Liu, Y. Li, J. Li, Z. Xie, Y. Wang, Z. Chen, *Nanomedicine (Lond)* **2019**, *14*, 19.
- [355] K. Yu, Y. Ding, H. Yu, W. Zhu, H. Yu, Y. Luo, X. Zheng, Y. Huang, Z. Lu, X. Wang, *ACS Sens.* **2022**, *7*, 1867.
- [356] T. Zhou, L. Wu, N. Ma, F. Tang, J. Chen, Z. Jiang, Y. Li, T. Ma, N. Yang, Z. Zong, *Bioeng. Transl. Med.* **2022**, *8*, e10368.
- [357] K. S Allermailem, A. Almatroudi, F. Alrumaihi, S. A Almatroodi, M. O Alkurbi, G. T. Basfar, A. H. Rahmani, A. A. Khan, *Int J Nanomedicine* **2021**, *16*, 5065.
- [358] B. Alharbi, H. Qanash, N. K. Binsaleh, S. Alharthi, A. M. Elasbali, C. H. Gharekhan, M. Mahmoud, E. Lioudakis, J. J. O'leary, D. G. Doherty, B. M. Mohamed, S. G. Gray, *Sci. Rep.* **2023**, *13*, 7462.
- [359] J. Gao, T. Luan, J. Lv, M. Yang, H. Li, Z. Yuan, *J Photochem Photobiol B* **2023**, *241*, 112666.
- [360] X. He, B. Xu, A. Fang, X. Li, Z. Huang, S. Qin, W. Xiao, G. Li, M. Tian, N. Fan, X. Song, *Acta Biomater.* **2023**, *162*, 120.
- [361] Y. Qing, Y. Guo, Q. Zhao, P. Hu, H. Li, X. Yu, M. Zhu, H. Wang, Z. Wang, J. Xu, Q. Guo, H. Hui, *Clin. Transl. Med.* **2023**, *13*, e1229.
- [362] N. Seebacher, D. J. R. Lane, D. R. Richardson, P. J. Jansson, *Free Radic Biol Med.* **2016**, *96*, 432.
- [363] D. De Clerk, R. Honeywell, G. Jansen, G. Peters, *Cancers (Basel)* **2018**, *10*, 503.
- [364] D.-Y. Hou, M.-D. Wang, N.-Y. Zhang, S. Xu, Z.-J. Wang, X.-J. Hu, G.-T. Lv, J.-Q. Wang, M.-Y. Lv, L. Yi, L. Wang, D.-B. Cheng, T. Sun, H. Wang, W. Xu, *Nano Lett.* **2022**, *22*, 3983.
- [365] Y. Yang, H. Ning, T. Xia, J. Du, W. Sun, J. Fan, X. Peng, *Adv. Mater.* **2023**, 2301409.
- [366] Y. Sun, Y. Sha, G. Cui, F. Meng, Z. Zhong, *Adv Drug Deliv Rev.* **2023**, *192*, 114624.
- [367] P. Liang, Y. Zhang, B. F Schmidt, B. Ballou, W. Qian, Z. Dong, J. Wu, L. Wang, M. P Bruchez, X. Dong, *Small* **2023**, *19*, e2207535.
- [368] Y. Chen, Z. Yang, S. Wang, Q. Ma, L. Li, X. Wu, Q. Guo, L. Tao, X. Shen, *Adv. Healthcare Mater.* **2023**, *12*, e2202150.
- [369] J. Liu, Y. Huang, T. Li, Z. Jiang, L. Zeng, Z. Hu, *Int J Mol Med.* **2021**, *47*, 38.
- [370] M. Martins, A. S. Fernandes, N. Saraiva, *Int. J. Biochem. Cell Biol.* **2022**, *145*, 106174.
- [371] P. Kulkarni-Gosavi, C. Makhoul, P. A. Gleeson, *FEBS Lett.* **2019**, *593*, 2289.
- [372] S. Sechi, A. Frappaolo, A. Karimpour-Ghahnavieh, R. Piergentili, M. G. Giansanti, *Int. J. Mol. Sci.* **2020**, *21*, 933.
- [373] Y. Xia, Y. Zhang, M. Shen, H. Xu, Z. Li, N. He, *Cell Prolif.* **2019**, *52*, e12538.
- [374] X. Zhang, *Front Cell Dev Biol.* **2021**, *9*, 665289.
- [375] F. Hamester, K. Legler, B. Wichert, N. Kelle, K. Eylmann, M. Rossberg, Y. Ding, S. Kürti, B. Schmalfeldt, K. Milde-Langosch, L. Oliveira-Ferrer, *Br. J. Cancer* **2019**, *121*, 944.
- [376] B. A. Flood, E. F. Higgs, S. Li, J. J. Luke, T. F. Gajewski, *Immunol Rev.* **2019**, *290*, 24.
- [377] Z. Y. Lee, J. S. E. Loo, A. Wibowo, M. F. Mohammat, J. B. Foo, *Carbohydr. Res.* **2021**, *508*, 108395.
- [378] R. ajaj, A. N. Warner, J. F. Fradette, D. L. Gibbons, *Cells* **2022**, *11*, 1484.
- [379] J. Li, E. Ahat, Y. Wang, *Results Probl Cell Differ.* **2019**, *67*, 441.
- [380] H.-M. Han, C. Bouchet-Marquis, J. Huebinger, M. Grabenbauer, *Histochem. Cell Biol.* **2013**, *140*, 369.
- [381] H. Xu, W. Su, M. Cai, J. Jiang, X. Zeng, H. Wang, *PLoS One* **2013**, *8*, e61596.
- [382] K. Matsuura-Tokita, M. Takeuchi, A. Ichihara, K. Mikuriya, A. Nakano, *Nature* **2006**, *441*, 1007.
- [383] K. Kurokawa, M. Ishii, Y. Suda, A. Ichihara, A. Nakano, *Methods Cell Biol.* **2013**, *118*, 235.
- [384] T. P. Foster, *Methods Mol Biol.* **2022**, *2422*, 85.
- [385] Y. Y. Wei, L. Chen, X. Zhang, J. L. Du, Q. Li, J. Luo, X. G. Liu, Y. Z. Yang, S. P. Yu, Y. D. Gao, *Biomater. Sci.* **2022**, *10*, 4345.
- [386] X. Rong, C. Liu, M. Li, H. Zhu, Y. Zhang, M. Su, X. Wang, X. Li, K. Wang, M. Yu, W. Sheng, B. Zhu, *Anal. Chem.* **2021**, *93*, 16105.
- [387] M. M. Fortibui, W. Lim, S. Lee, S. Park, J. Kim, *Molecules* **2021**, *26*, 4980.
- [388] C. Luchsinger, M. Aguilar, P. V. Burgos, P. Ehrenfeld, G. A. Mardones, *PLoS One* **2018**, *13*, e0195401.
- [389] M. Zhang, N. Xu, W. Xu, G. Ling, P. Zhang, *Pharmacol Res.* **2022**, *175*, 105861.
- [390] H. Li, C. Deng, Y. Tan, J. Dong, Y. Zhao, X. Wang, X. Yang, J. Luo, H. Gao, Y. Huang, Z.-R. Zhang, T. Gong, *Acta Biomater.* **2022**, *146*, 357.
- [391] C. H. Li, R. S. Li, C. M. Li, C. Z. Huang, S. J. Zhen, *Chem Commun (Camb)* **2019**, *55*, 6437.
- [392] L. Chen, P. Jiang, X. Shen, J. Lyu, C. Liu, L. Li, Y. Huang, *Small* **2023**, *19*, e2204747.
- [393] S. Zalba, T. L. M. Ten Hagen, *Cancer Treat. Rev.* **2017**, *52*, 48.
- [394] H.-S. Kim, Y. M. Shin, S. Chung, D. Kim, D. B. Park, S. Baek, J. Park, S. Y. Kim, D.-H. Kim, S. W. Yi, S. Lee, J. B. Lee, J.-Y. Ko, G.-I. Im, M.-L. Kang, H.-J. Sung, *Adv. Mater.* **2021**, *33*, 2101558.
- [395] L. Aloj, B. Attili, D. Lau, C. Caraco, L. M. Lechermann, I. A. Mendichovszky, I. Harper, H. Cheow, R. T. Casey, E. Sala, F. J. Gilbert, F. A. Gallagher, *Nucl. Med. Biol.* **2021**, *92*, 53.
- [396] J. Niu, Z. Li, *Cancer Lett.* **2017**, *403*, 128.
- [397] M. Hassn Mesrati, S. E. Syafuddin, M. A. Mohtar, A. Syahir, *Biomolecules* **2021**, *11*, 1850.
- [398] M. Brindisi, M. Curcio, L. Frattaruolo, G. Cirillo, A. Leggio, V. Rago, F. P. Nicoletta, A. R. Cappello, F. lemma, *Int. J. Biol. Macromol.* **2022**, *221*, 1491.
- [399] A. G. Wibmer, I. A. Burger, E. Sala, H. Hricak, W. A. Weber, H. A. Vargas, *Radiographics* **2016**, *36*, 142.
- [400] M. R. Juntila, F. J. De Sauvage, *Nature* **2013**, *501*, 346.
- [401] J. Yin, L. Huang, L. Wu, J. Li, T. D. James, W. Lin, *Chem. Soc. Rev.* **2021**, *50*, 12098.
- [402] Q. Li, W. Zhu, S. Gong, S. Jiang, G. Feng, *Anal. Chem.* **2023**, *95*, 7254.
- [403] Q. Li, J. Hong, S. Feng, S. Gong, G. Feng, *Anal. Chem.* **2022**, *94*, 11089.
- [404] S. Wu, Y. Yan, H. Hou, Z. Huang, D. Li, X. Zhang, Y. Xiao, *Anal. Chem.* **2022**, *94*, 11238.
- [405] S. Feng, Y. Liu, Q. Li, Z. Gui, G. Feng, *Anal. Chem.* **2022**, *94*, 1601.
- [406] B. Yao, L. Wang, C. Xie, M. Li, C. Peng, Z. Li, W. Lu, J. Chen, *Nucl. Med. Biol.* **2023**, *118-119*, 108330.
- [407] Y.-N. Ren, C. Liu, T. Liu, X. Duan, Q. Zhang, J. Liu, P. Wang, Q. Guo, X. Yang, P. Du, H. Zhu, Z. Yang, *Front Oncol.* **2022**, *12*, 1030187.

- [408] M. Lin, J. Zhang, H. Wan, C. Yan, F. Xia, *ACS Appl. Mater. Interfaces* **2021**, *13*, 9369.
- [409] Z. Hussain, M. A. Rahim, N. Jan, H. Shah, M. Rawas-Qalaji, S. Khan, M. Sohail, H. E. Thu, N. A. Ramli, R. M. Sarfraz, M. A. S. Abourehab, *J. Control. Release Off. J. Control. Release Soc.* **2021**, *335*, 130.
- [410] J. Liu, X. Xie, J. Lu, Y. He, D. Shao, F. Chen, *Pharmaceutics* **2022**, *14*, 2284.
- [411] Z. Wang, C. Zhao, Y. Li, J. Wang, D. Hou, L. Wang, Y. Wang, X. Wang, X. Liu, H. Wang, W. Xu, *Adv. Mater.* **2023**, 2210732.
- [412] Y. Feng, B. Wang, Y. Cao, R. He, *Med Hypotheses* **2013**, *80*, 380.
- [413] W. Xu, J. Wang, L. Jin, Y. Zhu, X. Yang, *Biomaterials* **2021**, *276*, 121024.
- [414] C. Zhang, F. Gao, W. Wu, W.-X. Qiu, L. Zhang, R. Li, Z.-N. Zhuang, W. Yu, H. Cheng, X.-Z. Zhang, *ACS Nano* **2019**, *13*, 11249.
- [415] P. Fan, Y. Guan, X. Zhang, J. Wang, Y. Xu, B. Song, S. Zhang, H. Wang, Y. Liu, Z. Y. Qiao, *Nanoscale Horiz.* **2023**.
- [416] J. C. Harris, M. A. Scully, E. S. Day, *Cancers (Basel)* **2019**, *11*, 1836.
- [417] Y. Wu, S. Wan, S. Yang, H. Hu, C. Zhang, J. Lai, J. Zhou, W. Chen, X. Tang, J. Luo, X. Zhou, L. Yu, L. Wang, A. Wu, Q. Fan, J. Wu, J. Nanobiotechnology **2022**, *20*, 542.
- [418] Y. Jiang, N. Krishnan, J. Zhou, S. Chekuri, X. Wei, A. V. Kroll, C. L. Yu, Y. Duan, W. Gao, R. H. Fang, L. Zhang, *Adv. Mater.* **2020**, *32*, 2001808.
- [419] J. Cui, F. Zhang, D. Yan, T. Han, L. Wang, D. Wang, B. Z. Tang, *Adv. Mater.* **2023**, 2302639.
- [420] F. Oroojalian, M. Beygi, B. Baradaran, A. Mokhtarzadeh, M.-A. Shahbazi, *Small* **2021**, *17*, e2006484.
- [421] Y. Tang, H. K. Bisoyi, X.-M. Chen, Z. Liu, X. Chen, S. Zhang, Q. Li, *Adv. Mater.* **2023**, *35*, 2300232.
- [422] W.-N. Zhao, M. Wang, C. Zhang, S. Sun, Y. Xu, *Chem Commun (Camb)* **2022**, *58*, 8512.
- [423] Y. Wang, A. Minden, *Int. J. Mol. Sci.* **2022**, *23*, 11046.
- [424] G. Wei, Y. Wang, G. Yang, Y. Wang, R. Ju, *Theranostics* **2021**, *11*, 6370.
- [425] H. Chen, Y. Wang, Y. Yao, S. Qiao, H. Wang, N. Tan, *Theranostics* **2017**, *7*, 3781.
- [426] T. Luo, Y. Fan, J. Mao, X. Jiang, L. Albano, E. Yuan, T. Germanas, W. Lin, *Angew Chem Int Ed Engl.* **2023**, *62*, e202301910.
- [427] J. Zhu, K. Zhang, Y. Zhou, R. Wang, L. Gong, C. Wang, K. Zhong, W. Liu, F. Feng, W. Qu, *ACS Appl. Mater. Interfaces* **2023**, *15*, 22403.
- [428] B. Wang, J. Fu, T. Yu, A. Xu, W. Qin, Z. Yang, Y. Chen, H. Wang, *Hepatology* **2018**, *67*, 623.
- [429] A. Mallick, P. More, S. Ghosh, R. Chippalkatti, B. A. Chopade, M. Lahiri, S. Basu, *ACS Appl. Mater. Interfaces* **2015**, *7*, 7584.
- [430] Y. Yao, J. Tao, J. Lyu, C. Chen, Y. Huang, Z. Zhou, *ACS Appl. Mater. Interfaces* **2023**, *15*, 20774.
- [431] B. Huang, H. Babcock, X. Zhuang, *Cell* **2010**, *143*, 1047.
- [432] J. Dai, Z. Wu, D. Li, G. Peng, G. Liu, R. Zhou, C. Wang, X. Yan, F. Liu, P. Sun, J. Zhou, G. Lu, *Biosens. Bioelectron.* **2023**, *229*, 115243.
- [433] R. Lee, J. A. Erstling, J. A. Hinckley, D. V. Chapman, U. B. Wiesner, *Adv. Funct. Mater.* **2021**, *31*, 2106144.
- [434] J. A. Erstling, J. A. Hinckley, N. Bag, J. Hersh, G. B. Feuer, R. Lee, H. F. Malarkey, F. Yu, K. Ma, B. A. Baird, U. B. Wiesner, *Adv. Mater.* **2021**, *33*, 2006829.
- [435] N. Serov, V. Vinogradov, *Adv Drug Deliv Rev.* **2022**, *184*, 114194.
- [436] X. He, X. Liu, F. Zuo, H. Shi, J. Jing, *Semin. Cancer Biol.* **2023**, *88*, 187.
- [437] P. Jiang, S. Sinha, K. Aldape, S. Hannenhalli, C. Sahinalp, E. Ruppin, *Nat. Rev. Cancer* **2022**, *22*, 625.
- [438] S. Z. Alshawwa, A. A. Kassem, R. M. Farid, S. K. Mostafa, G. S. Labib, *Pharmaceutics* **2022**, *14*, 883.
- [439] B. Govindan, M. A. Sabri, A. Hai, F. Banat, M. A. Haija, *Pharmaceutics* **2023**, *15*, 868.
- [440] Y. He, Z. Ye, X. Liu, Z. Wei, F. Qiu, H.-F. Li, Y. Zheng, D. Ouyang, *J. Control Release* **2020**, *322*, 274.
- [441] Z. Zheng, Y. Bian, Y. Zhang, G. Ren, G. Li, *Cell Cycle* **2020**, *19*, 1089.
- [442] P. Sharma, S. Kumar, *Cell Oncol (Dordr)* **2018**, *41*, 637.
- [443] T. Deguchi, K. Hosoya, S. Kim, Y. Murase, K. Yamamoto, T. Bo, H. Yasui, O. Inanami, M. Okumura, *Mol Ther Oncolytics* **2021**, *22*, 143.
- [444] W. Lee, G. Song, H. Bae, *Mar Drugs* **2022**, *20*, 473.
- [445] S. Wang, Z. Wang, L. Boise, P. Dent, S. Grant, *Leukemia* **1999**, *13*, 1564.
- [446] M. Kheirandish-Rostami, M. H. Roudkenar, A. Jahanian-Najafabadi, K. Tomita, Y. Kuwahara, T. Sato, A. M. Roushandeh, *Life Sci.* **2020**, *244*, 117339.
- [447] Y.-Z. Jin, Y.-X. Gong, Y. Liu, D.-P. Xie, C.-X. Ren, S.-J. Lee, H.-N. Sun, T. Kwon, D.-Y. Xu, *Anticancer Res.* **2021**, *41*, 1831.
- [448] Y.-P. Chen, P.-C. Shih, C.-W. Feng, C.-C. Wu, K.-H. Tsui, Y.-H. Lin, H.-M. Kuo, Z.-H. Wen, *Antioxidants (Basel)* **2021**, *10*, 1883.
- [449] W. Wang, M. Zhu, Z. Xu, W. Li, X. Dong, Y. Chen, B. Lin, M. Li, *Biol. Res.* **2019**, *52*, 36.
- [450] T. Capeloa, J. Krzystyniak, A. C. Rodriguez, V. L. Payen, L. X. Zampieri, E. Pranzini, F. Derouane, T. Vazeille, C. Bouzin, F. P. Duhoux, M. P. Murphy, P. E. Porporato, P. Sonveaux, *Cancers (Basel)* **2022**, *14*, 1488.
- [451] T. Capeloa, J. Krzystyniak, D. D'hose, A. Canas Rodriguez, V. L. Payen, L. X. Zampieri, J. A. Van De Velde, Z. Benyahia, E. Pranzini, T. Vazeille, M. Fransolet, C. Bouzin, D. Brusa, C. Michiels, B. Gallez, M. P. Murphy, P. E. Porporato, P. Sonveaux, *Cancers (Basel)* **2022**, *14*, 1516.
- [452] T. Capeloa, J. A. Van De Velde, D. D'hose, S. G. Lipari, F. Derouane, L. Hamelin, M. Bedin, T. Vazeille, F. P. Duhoux, M. P. Murphy, P. E. Porporato, B. Gallez, P. Sonveaux, *Cancers (Basel)* **2022**, *14*, 4918.
- [453] M. Lee, C. Yang, S. Park, G. Song, W. Lim, *J. Cell. Biochem.* **2022**, *123*, 469.
- [454] X. Zou, J. Liang, J. Sun, X. Hu, L. Lei, D. Wu, L. Liu, *J. Pharmacol. Sci.* **2016**, *131*, 233.
- [455] Y. Jin, D. T. N. Huynh, K.-S. Heo, *Arch. Pharm. Res.* **2022**, *45*, 174.
- [456] G. H. Jo, G.-Y. Kim, W.-J. Kim, K. Y. Park, Y. H. Choi, *Int J. Oncol.* **2014**, *45*, 1497.
- [457] Y. J. Lee, K. S. Park, S. H. Lee, *Biomed. Res. Int.* **2021**, *2021*, 8859181.
- [458] Y. Chen, J. Yang, Y. Zuo, C. Zhang, Y. Pu, Q. Ren, X. Li, Y. Huang, H. Huang, H. Yang, O. You, X. Xia, A. Lu, S. Shi, Y. Deng, J. Lu, *Pharmacol. Res.* **2022**, *184*, 106415.
- [459] M. Rasheduzzaman, J.-K. Jeong, S.-Y. Park, *Life Sci.* **2018**, *208*, 208.
- [460] X. Chen, Y. Zhao, W. Luo, S. Chen, F. Lin, X. Zhang, S. Fan, X. Shen, Y. Wang, G. Liang, *Theranostics* **2020**, *10*, 10290.
- [461] M. Yin, J. Dong, C. Sun, X. Liu, Z. Liu, L. Liu, Z. Kuang, N. Zhang, D. Xiao, X. Zhou, H. Deng, *Adv. Sci. (Weinh)* **2023**, *10*, e2206737.
- [462] K. C. Lee, C. Maturo, C. N. Perera, J. Luddy, R. Rodriguez, R. Shorr, *Ann. Transl. Med.* **2014**, *2*, 91.
- [463] J. R. Molina, Y. Sun, M. Protopopova, S. Gera, M. Bandi, C. Bristow, T. McAfoss, P. Morlacchi, J. Ackroyd, A.-N. A. Agip, G. Al-Atrash, J. Asara, J. Bardenhagen, C. C. Carrillo, C. Carroll, E. Chang, S. Ciurea, J. B. Cross, B. Czako, A. Deem, N. Daver, J. F. De Groot, J.-W. Dong, N. Feng, G. Gao, J. Gay, M. G. Do, J. Greer, V. Giuliani, J. Han, et al., *Nat. Med.* **2018**, *24*, 1036.
- [464] R. M. Thompson, D. Dytfield, L. Reyes, R. M. Robinson, B. Smith, Y. Manevich, A. Jakubowiak, M. Komarnicki, A. Przybylowicz-Chalecka, T. Szczepaniak, A. K. Mitra, B. G. Van Ness, M. Luczak, N. G. Dolloff, *Oncotarget* **2017**, *8*, 35863.
- [465] X. Shi, T. Zhang, H. Lou, H. Song, C. Li, P. Fan, *J. Med. Chem.* **2020**, *63*, 11786.
- [466] L. Chan, Y. Pang, Y. Wang, D. Zhu, A. Taledaohan, Y. Jia, L. Zhao, W. Wang, *Pharm. Biol.* **2022**, *60*, 1876.
- [467] H. Wen, S. Zhou, J. Song, *Biochem. Biophys. Res. Commun.* **2019**, *508*, 1271.
- [468] F. Ke, J. Yu, W. Chen, X. Si, X. Li, F. Yang, Y. Liao, Z. Zuo, *Biochem. Biophys. Res. Commun.* **2018**, *504*, 374.

- [469] Y. Chen, J. Zhang, M. Zhang, Y. Song, Y. Zhang, S. Fan, S. Ren, L. Fu, N. Zhang, H. Hui, X. Shen, *Clin. Transl. Med.* **2021**, *11*, e577.
- [470] C. Gao, L. Lin, W. Sun, Z.-L. Tan, J.-R. Huang, L. He, Z.-L. Lu, *Talanta* **2018**, *176*, 382.
- [471] J. Zhang, H. Shi, C. Huang, L. Mei, Q. Guo, K. Cheng, P. Wu, D. Su, Q. Chen, S. Gan, C. K. Wing Chan, J. Shi, J. L. Chen, C. H. Jonathan Choi, S. Q. Yao, X.-K. Chen, B. Z. Tang, J. He, H. Sun, *ACS Nano* **2023**, *17*, 3632.
- [472] Y. Huang, B. Song, K. Chen, Z. Tang, H. Ma, D. Kong, Q. Liu, J. Yuan, *Anal. Chem.* **2023**, *95*, 4024.
- [473] W. Ai, Y. Bu, H. Huang, J. Wang, M. Ren, Y. Deng, Y. Zhu, S. Wang, Z.-P. Yu, H. Zhou, *Anal. Chem.* **2023**, *95*, 6287.
- [474] Y. Cheng, A. E. Clark, J. Zhou, T. He, Y. Li, R. M. Borum, M. N. Creyer, M. Xu, Z. Jin, J. Zhou, W. Yim, Z. Wu, P. Fajtová, A. J. O'donoghue, A. F. Carlin, J. V. Jokerst, *ACS Nano* **2022**, *16*, 12305.
- [475] Z. Liu, Q. Wang, H. Wang, W. Su, S. Dong, *Sensors (Basel)* **2020**, *20*, 1746.
- [476] S.-K. Choi, J. Rho, S. E. Yoon, J.-H. Seok, H. Kim, J. Min, W. Yoon, S. Lee, H. Yun, O.-P. Kwon, J. H. Kim, W. Kim, E. Kim, *Biocorjug Chem.* **2020**, *31*, 2522.
- [477] Z. Ye, L. Wei, X. Geng, X. Wang, Z. Li, L. Xiao, *ACS Nano* **2019**, *13*, 11593.
- [478] L. Zhao, Z. Huang, D. Ma, Y. Yan, X. Zhang, Y. Xiao, *Analyst* **2021**, *146*, 4130.
- [479] W. Sun, J.-X. Cui, L.-L. Ma, Z.-L. Lu, B. Gong, L. He, R. Wang, *Analyst* **2018**, *143*, 5799.
- [480] C. Shi, Y. Wang, X. Tian, X. Lv, Y. An, J. Ning, X. Xin, L. Dai, X. Ma, L. Feng, *Molecules* **2023**, *28*, 3472.
- [481] S.-Z. Liu, J.-H. Xu, Q.-J. Ma, B.-Y. Wang, L.-K. Li, N.-N. Zhu, S.-Y. Liu, G.-G. Wang, *Spectrochim Acta A Mol Biomol Spectrosc.* **2023**, *286*, 121986.



Yongqing Tong obtained his M.D. and Ph.D. degrees from Central South University in 2008. He was a postdoctoral researcher at Penn State College of Medicine from 2014 to 2015. He is now a Chief physician in the Department of Clinical Laboratory, Renmin Hospital of Wuhan University. His research interest is in clinical molecular diagnostics, including cancer, genetic diseases, infectious diseases, and prenatal diagnosis, et al.



Yan Ma, Ph.D., is Director of the Blood Optical Imaging Technology Center and Deputy Director of the Blood Transfusion Research Laboratory of Wuhan Blood Center. His research encompasses the study of platelet-related diseases and the development of targeted fluorescent small molecules associated with them, the exploration of novel drug delivery systems, the advancement of subcellular structural optical imaging techniques, as well as the development of new methods for blood testing in major diseases such as cancer and cardiovascular disorders.



Anyu Bao obtained his M.D. and Ph.D. degrees from Wuhan University in 2014. He is now a Chief physician and Associate Professor in Renmin Hospital of Wuhan University. He works in the Clinical Laboratory of the hospital and his research interest mainly focuses on the molecular diagnosis and liquid biopsy of cancer. He has been exploring novel molecules and efficient methods for the rapid diagnosis and evaluation of therapeutic effects of cancer.