




Recent Progress in Peptide-Based Fluorescent Probes Biomedical Applications: A Review

Xue Zhong ^{1,2,*}, Yuanlong Xie ^{1,*}, Yuen Chen², Yushen Lu², Mingming Hou ³

¹Department of Spine Surgery and Musculoskeletal Tumor, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, People's Republic of China; ²Second Clinical College, Wuhan University, Wuhan, Hubei, People's Republic of China; ³Department of Orthopedics, Honghui Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, People's Republic of China

*These authors contributed equally to this work

Correspondence: Mingming Hou, Department of Orthopedics, Honghui Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, People's Republic of China, Email whuhm@126.com

Abstract: Peptide-based fluorescent probes have found widespread applications in biomedical research, including bio-imaging, disease diagnosis, drug discovery, and image-guided surgery. Their favorable properties—such as small molecular size, low toxicity, minimal immunogenicity, and high targeting specificity—have contributed to their growing utility in both basic research and translational medicine. This review provides a comprehensive overview of recent advances in peptide-based fluorescent probes, emphasizing design strategies, biological targets, and diverse functional applications. Key areas of focus include the integration of molecular targeting with imaging capabilities, the emergence of multimodal imaging techniques, and the development of activatable probes responsive to specific biological stimuli. Applications are discussed in the context of tumor cell membrane recognition, subcellular organelle targeting, non-cancer disease diagnosis, and detection of both metal ions and non-metal ions. Notably, responsive probes for reactive oxygen species (ROS) and other biologically relevant non-metal ions are also highlighted, underscoring their diagnostic and therapeutic potential. The review also addresses key limitations—such as poor in vivo stability, limited targeting accuracy, and delivery efficiency—and outlines future directions including smart peptide probe platforms, self-reporting systems, and high-throughput screening based on peptide libraries to accelerate next-generation probe development.

Keywords: peptide fluorescent probes, drug-targeted delivery, bio-imaging, tumor cell identification, organelle targeting, metal ion detection, multimodal imaging

Introduction

Intraoperative navigation, surgical therapy, and tumor diagnostics all benefit significantly from advanced techniques capable of visualizing molecular and anatomical features in vivo. While conventional imaging methods such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and ultrasound remain widely used, they suffer from limitations in spatial and temporal resolution, sensitivity, and molecular-level specificity, making them suboptimal for real-time dynamic monitoring.

In contrast, molecular imaging using targeted probes provides a more accurate approach for visualizing complex biological processes at the cellular or subcellular level. For example, Tang et al synthesized a B7H3-targeted IRDye800CW probe that enabled precise labeling of osteosarcoma tissues and facilitated real-time intraoperative identification and resection of tumor margins.¹ Peptide molecules have recently emerged as a particularly promising class of imaging agents due to their small size, excellent target specificity, low immunogenicity, good permeability, and favorable biocompatibility. These properties make peptides ideal carriers for targeted fluorescent probes. Compared to antibodies and nanoparticles, peptide-based fluorescent probes offer several significant advantages, including lower immunogenicity, faster renal clearance, better tumor penetration, and easier synthesis and modification. In contrast to small-molecule probes, peptides exhibit enhanced specificity and affinity due to their ability to engage in multivalent interactions and form stable secondary structures that improve target recognition. These properties make peptides

particularly attractive for in vivo imaging applications where both biocompatibility and precision are critical. In parallel, advances in second near-infrared (NIR-II, 1000–1700 nm) fluorophores have further expanded the utility of in vivo imaging. For instance, Tang et al reported an intramolecular repulsive interaction (IRI)-based strategy to boost the luminescence efficiency of NIR-II aggregation-induced emission (AIE) materials.² A recent study also highlighted the multifunctional potential of peptide-based fluorescent probes in both tumor targeting and tumor microenvironment modulation, further expanding their biomedical applications,³ Despite the clinical potential of traditional dyes such as sodium fluorescein and indocyanine green (ICG),^{4,5} their poor targeting capacity remains a significant drawback. Peptide-based fluorescent probes—typically composed of a targeting peptide, a linker, and a fluorescent moiety—offer a viable solution, combining minimal immunogenicity, high targeting efficiency, and real-time visualization potential.⁶

This review aims to provide a comprehensive overview of recent progress in peptide-targeted fluorescent probes, with a specific focus on their applications in tumor imaging, organelle targeting, non-tumor disease diagnosis, metal ion detection, multimodal imaging, and drug-targeted delivery. We also highlight emerging strategies such as activatable probes and intelligent designs, and discuss existing challenges and translational potential. A general classification of peptide-based fluorescent probes is provided in Figure 1, serving as a conceptual framework for the topics covered.

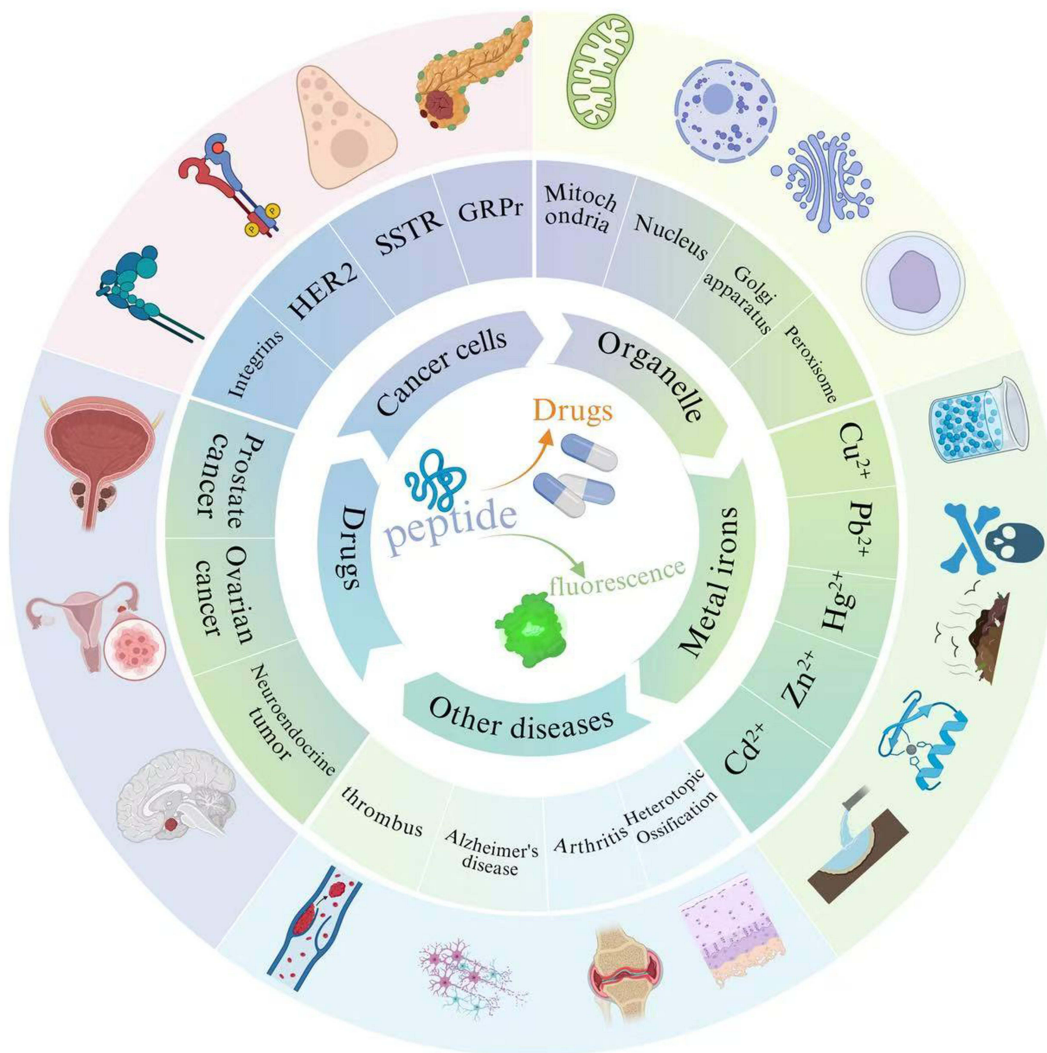


Figure 1 The classification of the peptide based fluorescent probes or drugs mentioned in this review. Created in BioRender. Peng, R. (2025) <https://BioRender.com/w88u512>.

Peptide Fluorescent Probes for Biological Targeting and Imaging

Peptide Fluorescent Targeting Tumor Cell Membrane Receptors

One of the key tactics for accurately diagnosing and treating malignant tumors is fluorescence navigation, particularly ICG-based near-infrared fluorescence navigation technology, which significantly improves surgical oncology precision and can raise patient survival and prognosis. Tumor-associated targets such as integrins, HER2, SSTR, and GRPR serve as important foundations for the development of peptide-based fluorescent probes due to their highly specific over-expression in various cancer cells. Integrins—especially $\alpha\beta3$ —promote tumor angiogenesis and migration; HER2 is highly expressed in breast and gastric cancers; SSTR2 is commonly found in neuroendocrine tumors; and GRPR is involved in cell proliferation in cancers such as pancreatic cancer, all demonstrating strong potential for imaging applications.^{7,8} There are several potential therapeutic applications for using these receptors to create tailored peptides and targeted peptide fluorescence probes. Peptide-based fluorescent probes targeting integrins, HER2, and GRPR demonstrate strong binding affinity, with examples such as KSP*-Cy5.5 showing a dissociation constant of 21 nM for HER2. These probes also exhibit excellent imaging stability—for instance, cRGD signals persist for over 24 hours, and the imaging window of ICG-Herceptin extends up to 8 hours. Compared to traditional dyes, peptide probes offer higher signal-to-noise ratios and lower background signals, with mechanisms like aggregation/assembly-induced retention (AIR) further enhancing tumor site accumulation.^{9,10} Additionally, multiple studies have confirmed their low toxicity and good biocompatibility, supporting their promising clinical potential.

Peptide Probes Targeting Integrins

Integrins are a broad family of transmembrane cell adhesion molecules that are classified as collagen receptors, leukocyte-specific receptors, arginine-glycine-aspartate (RGD)-binding receptors, and laminin receptors.¹¹ Malignant neovascular and tumor cells exhibit markedly elevated expression of these molecules.¹²

Because of its excellent binding specificity and stability, the tripeptide RGD and its cyclized variants (such as cRGDyK and cRGDfK) have found extensive application in targeted imaging and treatment.^{13,14} By creating a cyclized structure, cRGD makes the peptide more rigid, which enhances its stability and specificity of binding with integrin $\alpha\beta3$.

It has been demonstrated that $\alpha\beta3$ -positive glioma U87MG cells may efficiently absorb cRGD-PEG-siEGFR, which is produced by attaching the cyclic peptide via polyethylene glycol to a short interfering RNA that targets the epidermal growth factor receptor (EGFR), to provide anti-tumor effects.¹⁵

Regarding tumor imaging, the imaging probe of the NIR fluorescent cyclic RGD peptide produced by combining an aminated RGD peptide with a near-infrared (NIR) dye was able to enable targeted imaging of tumor endothelial cells with high expression of integrins.¹⁶

MMP2/9 enzymes are generally recognized as being involved in cancer metastasis and are regarded as biomarkers for malignant tumors. Based on this concept, an MMP2/9-responsive fluorescent probe has been designed for the selective detection of malignant tumor cells with high MMP2/9 expression and the conditional activation of reactive oxygen species (ROS) generation, enabling the integration of imaging and photodynamic therapy (PDT).

Utilizing the aggregation/assembly-induced retention (AIR) effect and the tumor-specific excretion-retarded (TER) effect, a near-infrared probe A has been developed to target integrin receptors on the surface of human renal cell carcinoma (RCC) and liver tumor cells. This probe is designed by integrating a targeting motif (RGD), an enzyme-responsive peptide ligand (PLGYLG), a self-assembly motif (YLGFFC), and a near-infrared signaling molecule (Cy). Initially, probe A selectively binds to the highly expressed $\alpha\beta3$ integrin in RCC, after which it is cleaved by MMP2/9 enzymes. The resulting fragments spontaneously self-assemble into nanofibers, facilitating high-performance detection of human RCC.¹⁷

MMP2/9 enzymes are widely recognized for their involvement in cancer metastasis and are considered biomarkers for malignant tumors. Accordingly, a responsive fluorescent probe incorporating an MMP2/9-cleavable peptide linker (Pro-Leu-Gly-Val-Arg-Gly) has been designed to enable the selective detection of malignant tumor cells with elevated MMP2/9 expression.¹⁸

Long-term cell labeling may be possible with dual-targeted fluorescence probes. With a peptide composition made up of cNGR (targeted cycling peptide motif), CPP (cell-penetrating peptide), and NLS (nuclear localization signal sequence), the dual-targeted multifunctional fluorescence probe (TCNTP) may be utilized for behavioral investigations

of cancer cells. In order to provide effective nucleus-specific imaging and long-term, low-toxicity monitoring of cancer cells, this probe combines a flexible delivery mechanism with the aggregation-induced luminescence of a tetrastylene derivative.¹⁹

Table 1 Summary of Tumor-Related Peptide Fluorescent Probes.

Peptide Fluorescent Probes Targeting Receptor 2 for Human Epidermal Growth Factor

The oncogene ERBB2 encodes the receptor known as HER2 (Human Epidermal Growth Factor Receptor 2), which is expressed on the surface of a wide range of tumor cells, including colorectal, liver, gastric, breast, and non-small cell lung (NSCLC) cancers, among many others.^{8,25,26}

A newly discovered peptide, Herceptide (RSLWSDFYASASRGP), was employed as the targeting moiety. The probe ICG-Herceptide, synthesized by conjugating Herceptide with ICG—a NIR(II) near-infrared fluorescent dye—exhibits excellent targeting ability, high specificity, and low biotoxicity. In *in vivo* mouse experiments, the probe effectively delineated the boundary between the tumor and adjacent tissues, providing valuable assistance in tumor resection.²⁰

Based on the targeting peptides RSLWSDFY, KSPNPRF, and RSLWSDFYKSPNPRF, three new HER2 targeting probes were created: DOTA-ZC01-ICG, DOTA-KSP-ICG, and DOTA-ZC02-ICG. When it came to HER2-positive tumors, DOTA-ZC02-ICG outperformed the others in terms of affinity and specificity and produced good bimodal imaging.²¹ A peptide with the sequence KSPNPRF, designed by Bishnu P. Joshi et al, was conjugated to the fluorescent dyes FITC or Cy5.5 via the linker GGGSK using Fmoc-mediated solid-phase synthesis, resulting in a fluorescent probe named KSP*-Cy5.5. This probe holds great potential as a powerful tool for the early detection of colon tumors.⁹

Peptide Fluorescent Probes Targeting the Growth Inhibitory Receptor

The growth inhibitory receptor (SSTR) is expressed in different parts of the brain, stomach, pituitary, endocrine, and adrenal glands at variable levels.²⁷ SSTR subtype 2 (SSTR2) is an ideal target for imaging and treating persons with neuroendocrine tumors (NETs) and neuroendocrine tumors in general.²⁸

Table 1 Summary of Tumor-Related Peptide Fluorescent Probes

Targeted Organelle/ Molecule	Probe Name/ Core	Peptide Sequence	Functional Features	Application	Ref.
Integrin $\alpha\beta 3$	cRGD, cRGDfK	Arg-Gly-Asp (cyclized)	Cyclization improves stability and specificity; long-lasting imaging signal	Targeted imaging and therapy	[13–16]
Integrin $\alpha\beta 3$ + EGFR	cRGD-PEG-siEGFR	cRGD + siRNA	Delivers siRNA for EGFR silencing; strong tumor targeting	Targeted RNAi therapy	[15]
Integrin $\alpha\beta 3$ + MMP2/9	Probe A	RGD + PLGYLG + YLGFFC	AIR effect; enzyme-triggered self-assembly into nanofibers	RCC tumor imaging	[17]
MMP2/9	MMP-responsive probe	Pro-Leu-Gly-Val-Arg-Gly	Activates ROS under MMP2/9 cleavage; combines imaging with PDT	Malignant tumor imaging + phototherapy	[18]
GRPR + Nucleus	TCNTP	cNGR + CPP + NLS	Dual-targeted; aggregation-induced emission (AIE); low-toxicity long-term labeling	Cancer cell tracking and imaging	[19]
HER2	ICG-Herceptide	RSLWSDFYASASRGP	ICG labeling; high specificity; clear tumor margins	HER2+ tumor boundary detection	[20]
HER2	DOTA-ZC01 /KSP/ZC02-ICG	RSLWSDFY / KSPNPRF / RSLWSDFYKSPNPRF	Dual-modality; strong HER2+ targeting and affinity	Molecular imaging of HER2+ tumors	[21]
HER2	KSP*-Cy5.5	KSPNPRF	High affinity; early-stage tumor detection	Early colon cancer detection	[9]
SSTR2	3207-86	(D)Phe-Cys*-Gly(S2)*-NH ₂	Cyclic peptide; D-amino acids improve affinity and stability	Neuroendocrine tumor imaging	[22]
SSTR2/5	Cy dye-conjugated cyclic peptide	H ₂ N-(D-Phe)-cyclo.[]	High specificity to SSTR subtypes; strong fluorescence properties	Targeted receptor imaging	[23]
GRPR	MPA-PEG ₄ -GB-6	Gln-Htp- β -Ala-Nva-Gly-His-NH ₂	Long-lasting NIR signal; selective GRPR targeting	GRPR-positive tumor imaging	[24]

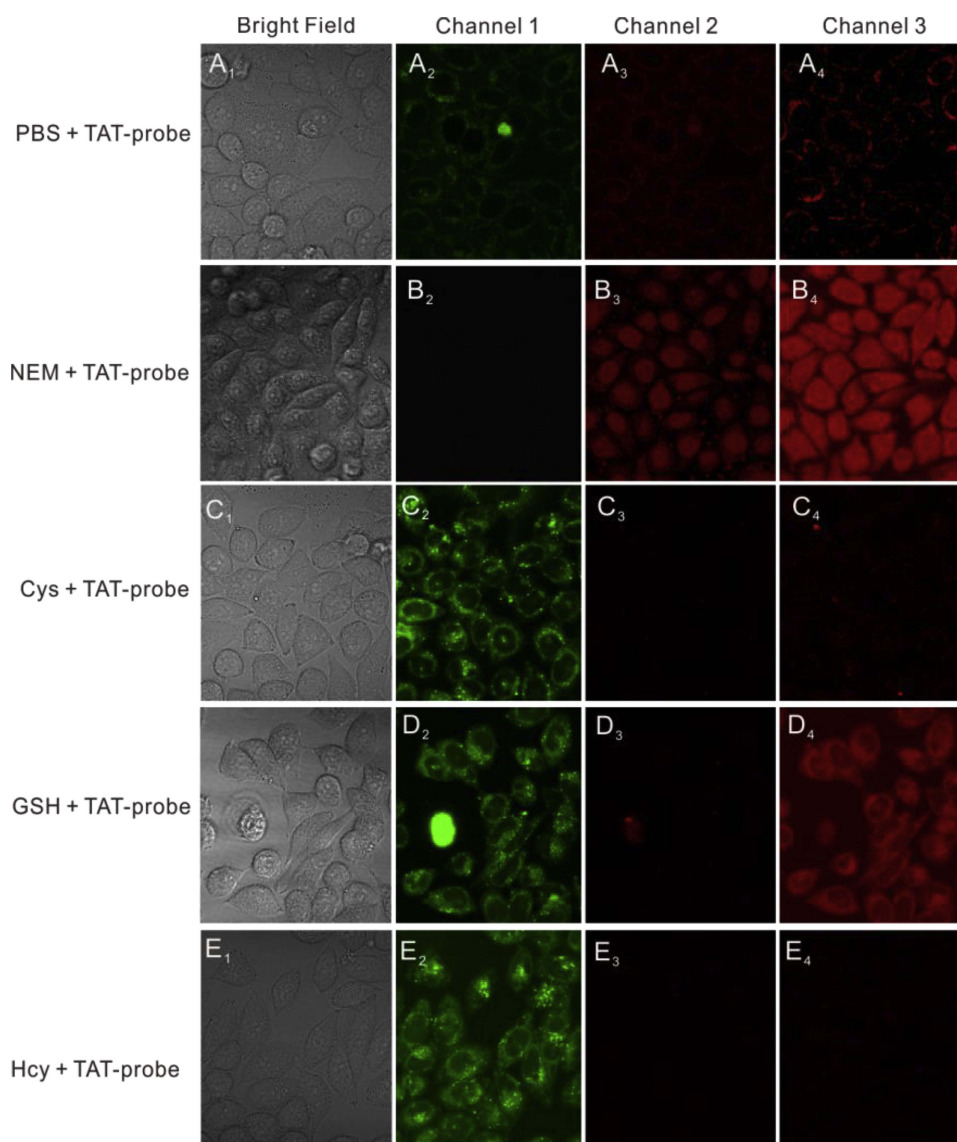


Figure 2 Two-photon confocal fluorescence imaging of HeLa cells treated with the TAT-based fluorescent probe (5 μ M) under different conditions: **(A)** PBS; **(B)** NEM (1 mM); **(C)** Cys (100 μ M); **(D)** GSH (100 μ M); **(E)** Hcy (100 μ M). (1) Bright-field images; (2) Channel 1: $\lambda_{\text{ex}} = 820$ nm, $\lambda_{\text{em}} = 520 \pm 10$ nm; (3) Channel 2: $\lambda_{\text{ex}} = 820$ nm, $\lambda_{\text{em}} = 585 \pm 10$ nm; (4) Channel 3: $\lambda_{\text{ex}} = 545$ nm, $\lambda_{\text{em}} = 585 \pm 10$ nm. Reprinted from *Talanta*, 218, Su P, Zhu Z, Tian Y, et al. A TAT peptide-based ratiometric two-photon fluorescent probe for detecting biothiols and sequentially distinguishing GSH in mitochondria, 121127, ©Copyright 2020 with permission from Elsevier. [DOI: 10.1016/j.talanta.2020.121907].³⁶

more suited for functional intervention, whilst the T-AIE-M structure showed greater tumor cell selectivity and was appropriate for targeted imaging.³⁰

Probes for Targeting the Nucleus

Disease phenotypes are strongly associated with changes in the nucleus's structure, and when it malfunctions, it can lead to conditions including Parkinson's, cancer, and retinitis pigmentosa.³⁷ As a result, nuclear tracking, nuclear treatment and illness diagnostics depend on fluorescent imaging probes that target the nucleus.

Cargo proteins can penetrate the nuclear membrane through negatively charged nuclear pore complexes mediated by nuclear localization signal peptides (NLS), which often comprise lengthy amino acid sequences of positively charged lysines or arginines.³⁸ NLS peptides can be used in this context as particular peptides that target the nucleus.

The photonic and two-photon fluorescence features of carbon dots (CDs), which are made from tryptophan and formic acid using a one-step hydrothermal process, have garnered a lot of interest in the bio-imaging community. The TAT peptide

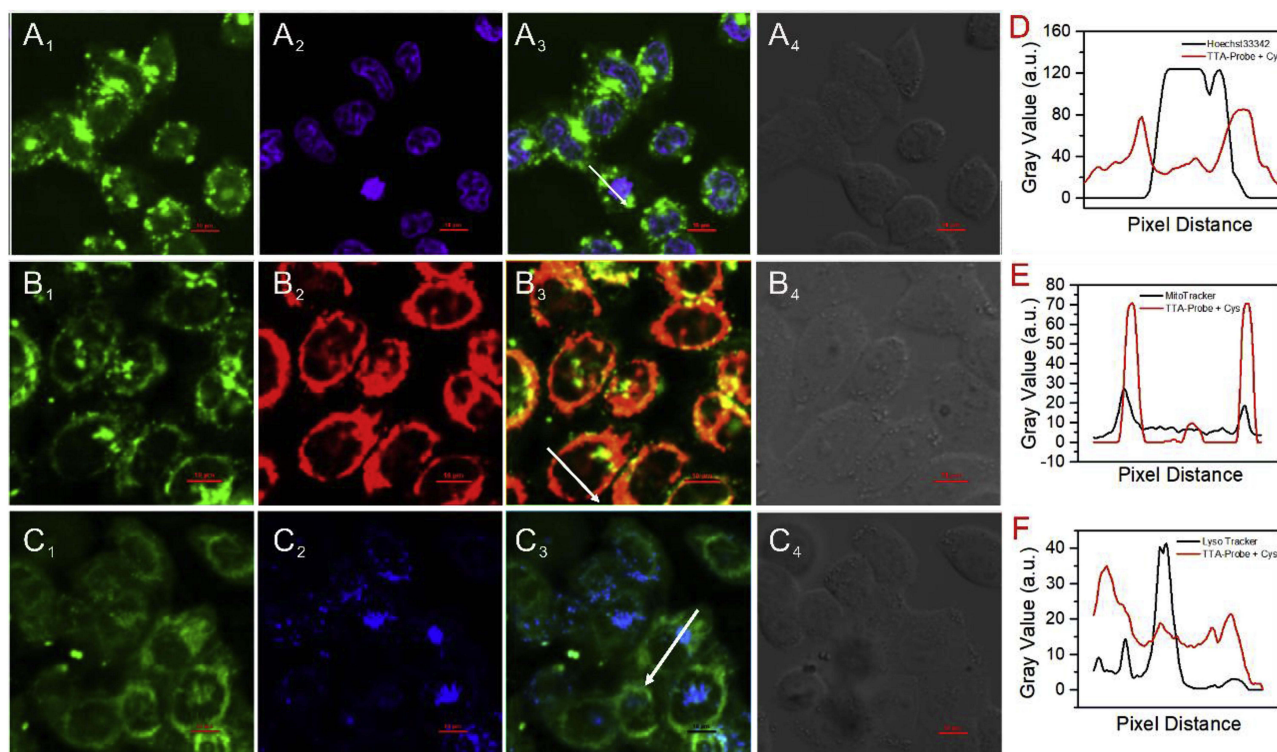


Figure 3 Subcellular localization of the TAT-probe (5 μM) in HeLa cells co-incubated with Cys (100 μM) and (A) Hoechst 33342 (100 nM); (B) MitoTracker Red; (C) LysoTracker (100 nM) for 30 min at 37 $^{\circ}\text{C}$. (1) TAT-probe fluorescence ($\lambda_{\text{ex}} = 820 \text{ nm}$, $\lambda_{\text{em}} = 520 \pm 10 \text{ nm}$); (2) Counterstaining channel; (3) Merged images; (4) Bright-field images. (D–F) Intensity profiles along the white arrows in merged images. Reprinted from *Talanta*, 218, Su P, Zhu Z, Tian Y, et al. A TAT peptide-based ratiometric two-photon fluorescent probe for detecting biothiols and sequentially distinguishing GSH in mitochondria, 121127, ©Copyright 2020 with permission from Elsevier. [DOI: 10.1016/j.talanta.2020.121907].³⁶

(GRKKRRQRRRPQ) is a nuclear localization signal peptide capable of traversing both the cellular and nuclear membranes. By coupling carbon dots with TAT peptides to form imaging probes (TAT-CDs), one-photon and two-photon nuclear-targeted fluorescence imaging can be achieved, offering valuable applications in disease diagnosis and therapeutic research.³⁹

Using citric acid, PEG, and ethylenediamine to create CDs@PEG that can precisely release intense blue fluorescence and then covalently attaching NLS peptides (PKKKRKVG) to the carbon dots to create NLS-CDs for nucleus-targeted imaging is another technique for creating probes.⁴⁰

Targeting hydrogen peroxide in the nucleus was made possible by the innovative use of the ratiometric fluorescent probe NP1. The nuclear localization signal peptide (NLS, sequence VQRKRQKLMP-NH₂) effectively directs the probe into the nucleus when combined with NP1, allowing for the accurate detection of hydrogen peroxide in the nucleus.⁴¹

Peptide Fluorescent Probes for Targeting the Golgi Apparatus

The Golgi is critical for maintaining cellular homeostase, and any dysfunction of the copper-transporting ATPase in the Golgi can disrupt copper homeostase, leading to neurodegenerative diseases, cancer, and more.^{42,43}

In order to detect Cu⁺ in the Golgi apparatus, the Dansyl-labeled tripeptide probe Dns-LLC was created. Its unique structure provides a potent tool for the study of Golgi function by binding Cu ions via sulfurhydryl groups and working in concert with dansulfonyl and amide groups to produce persistent fluorescent signals.⁴⁴

Furin protease is a Golgi-transported preprotein convertase, and new evidence indicates that Furin plays a key role in neurodegenerative and neuropsychiatric disorders, cancer, and infectious diseases.⁴⁵ Furin can be targeted by taking advantage of its specific cleavage of substrates (Arg-X-Arg/Lys-Arg↓) in the Golgi.⁴⁶

Due to the diffusive nature of the fluorescent molecules, existing probes against furin protease are challenging to detect and image in situ. Li et al responded by creating the HPQF probe, which uses the self-destructing linker piperidin-2-ylmethanamine to connect the RVRR peptide to Cl-HPQ. When transformed by furin, HPQF releases free Cl-HPQ and

Table 2 (Continued).

Targeted Organelle	Probe Name/Core Molecule	Peptide Sequence	Functional Features	Application	Ref.
Golgi apparatus	HPQF	RVRR	Furin-responsive self-precipitating fluorescence	Real-time furin imaging in situ	[47]
Golgi apparatus	HD-F	RVRR	NIR fluorescence; visualizes furin expression variation	Golgi furin detection	[48]
Golgi apparatus	C-3	RVRRFFF	Self-assembling nanostructure; long-term intracellular retention	Persistent furin tracking	[49]
Golgi apparatus	pSI / SI	D-ff + NBD	ALP-triggered self-assembly; accumulates in Golgi	Targeted cancer cell ablation	[50,51]
Peroxisome	PTS1 probe	CKGGAKL + PTS1	Efficient membrane penetration and peroxisome targeting	Imaging and metabolic disorder research	[53]

Notes: Summary of Peptide-Based Fluorescent Probes Targeting Organelles.

Multimodal Imaging Modalities Based on Peptide Fluorescent Probes

Due to its safety, high spatial resolution, and real-time performance, fluorescence imaging has become a widely used imaging technique for clinical tumor detection and image-guided surgery, in contrast to more conventional anatomical and molecular imaging methods like X-CT, PET, MRI, PAI, and USI.⁵⁴ Combining different imaging modalities has become a mainstream trend in disease diagnosis.⁵⁵ The process of creating images by combining chemical data from several platforms is known as multimodal imaging.⁵⁶ They are dual-labeled with a fluorescent contrast agent and a radioactive material, and they have specific locations. These substances can be utilized for surgically guided tumor removal and allow for intraoperative and whole-body imaging with a single dosage. Optical imaging offers high resolution but shallow penetration, whereas MRI provides deep tissue imaging with excellent anatomical detail. Combining modalities allows for comprehensive diagnostic information.⁵⁷ Multimodal probes enable more accurate tumor localization, intraoperative guidance, and real-time therapy monitoring, which are crucial for improving surgical outcomes and personalized treatment.⁵⁸ Despite their promise, challenges such as probe synthesis complexity, cost, and in vivo pharmacokinetics must be addressed for successful clinical translation.⁵⁹ For fluorescent probes involved in multimodal imaging, we have also created a schematic diagram (Figure 4).

Combined with CT Imaging Modalities

There is significant promise for usage in the field of thrombus identification when peptide probes are combined with CT imaging methods that use nanoparticles as imaging contrast agents.^{60,61}

For dual-modal thrombus imaging employing near-infrared fluorescence (NIRF) and micro-computed tomography (micro-CT), Kwon et al synthesized a thrombin-activatable fluorescent peptide (TAP) and integrated it into silica-coated gold nanoparticles (TAP-SiO₂@AuNPs). The TAP molecules restore the NIRF signal by precisely targeting thrombin activity. Its potential for thrombus detection and treatment was highlighted by experimental results that showed considerable buildup at thrombus sites and good imaging performance. Figure 5 illustrates⁶² thrombus detection through TAP-SiO₂@AuNPs, showing thrombin-activated multimodal imaging capability.

Combined with PET Imaging Modality

Although PET imaging is renowned for its great sensitivity,⁶³ it is challenging to offer accurate anatomical information due to its lack of resolution restriction.⁶⁴ The diagnosis, staging, and border determination of malignant tumors have been successfully enhanced by integrating preoperative positron emission tomography (PET) and molecular probes with near-infrared fluorescence (NIRF)-guided imaging, which has increased the accuracy of surgical resection.⁶⁵

In a single probe, Peter S. Conti et al integrated fluorescence and PET imaging. After attaching the c(RGDyK)₂ peptide (denoted as RGD₂) to a Cy5.5 fluorescent dye with the chelator BaAn(Boc)Sar and labeling with ⁶⁴Cu, PET and fluorescence imaging were carried out. According to the experimental results, the probe had outstanding intraoperative

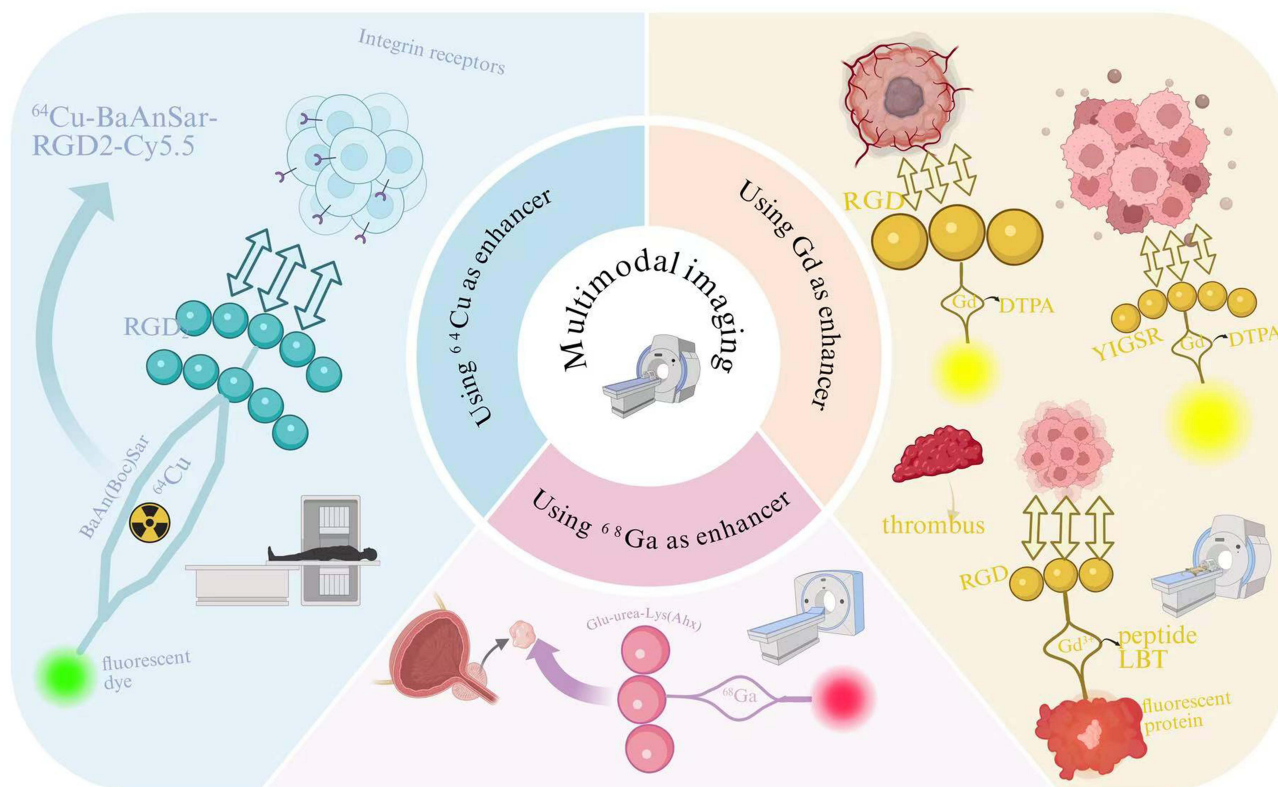


Figure 4 The structures of peptide-based fluorescent probes involved in multimodal imaging. Created in BioRender. Peng, R. (2025) <https://BioRender.com/k77a932>.

imaging ability and clinical translational potential, and it could efficiently and specifically recognize and bind to the integrin $\alpha v \beta 3$ receptor in PET and fluorescence imaging.⁶⁶

Ann-Christin Baranski et al employed the chelator HBED-CC to conjugate ^{68}Ga with the peptide Glu-urea-Lys(Ahx), which was subsequently coupled with fluorescent dyes (IRDye800CW, DyLight800) to synthesize the PSMA-targeting probe ^{68}Ga -Glu-urea-Lys-HBED-CC-IRDye800CW. This probe enables PET/fluorescence dual-modality imaging, offering a valuable tool for precise tumor visualization.⁶⁷

Combined with PAI Imaging Modality

In preclinical research, photoacoustic imaging (PAI) has demonstrated significant potential in delivering structural, functional, and molecular information.^{68,69} Recent years have also seen significant developments in the application of PAI in conjunction with other imaging modalities, particularly in tumor therapy. For instance, target-dependent photoacoustic signals can be produced using photoactivated probes.

Jelena Levi et al developed an activatable photoacoustic probe targeting matrix metalloproteinase-2 (MMP-2) for precise enzymatic activity detection. The probe utilizes the ACPD peptide (Ceeee[Ahx]PLGLAGrrrrrK), where, before cleavage, the photoacoustic signals of BHQ3 and Alexa750 cancel each other out. Upon MMP-2-mediated cleavage of the PLGLAG sequence, the BHQ3-labeled CPP portion accumulates inside cells, while Alexa750 diffuses away, resulting in photoacoustic signals only at 675 nm. Experimental results confirm that this probe is suitable for tumor microenvironment imaging and localization.⁷⁰

Combined with MRI Imaging Modalities

MRI/fluorescence imaging modalities have been developed and have shown complementary imaging properties including high sensitivity and high spatial resolution for precise tumor localization, strong penetration, powerful imaging modalities, and a wide range of applications.^{71,72}

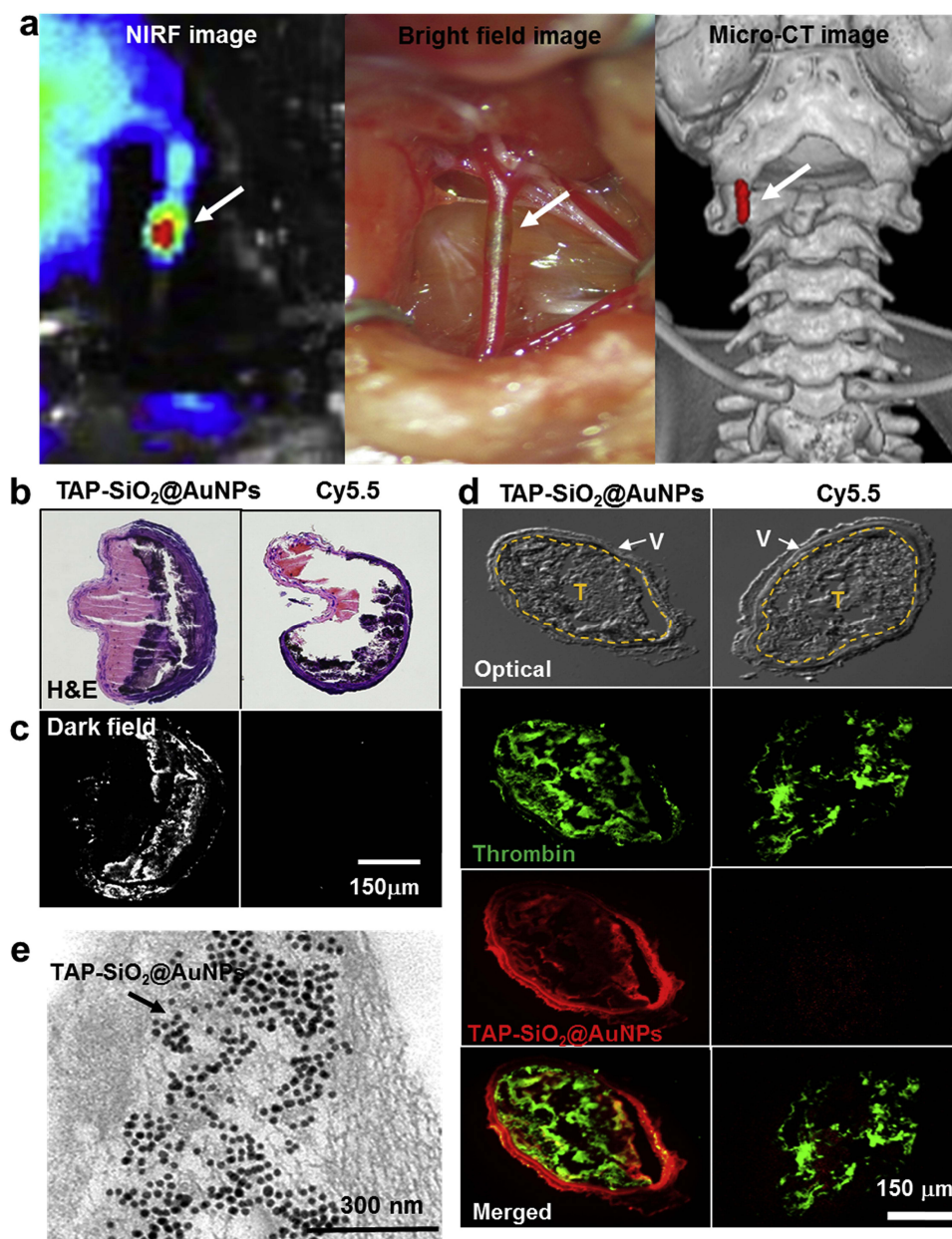


Figure 5 Multimodal thrombus imaging using thrombin-activatable fluorescent peptide-incorporated gold nanoparticles (TAP-SiO₂@AuNPs). (a) Dual-modality in vivo imaging (NIRF, bright-field, and micro-CT) of an in situ thrombotic mouse model treated with TAP-SiO₂@AuNPs, showing thrombus accumulation (white arrows). (b) H&E staining of dissected common carotid arteries (CCA) from mice treated with TAP-SiO₂@AuNPs or Cy5.5. (c) Dark-field imaging of the same samples. (d) Immunofluorescence imaging of thrombin activity (green) and nanoparticle distribution (red) in vessel cross-sections, with merged views showing thrombus localization. “V” indicates vessel endothelium, “T” indicates thrombus. (e) Transmission electron microscopy (TEM) image of the dissected CCA, confirming the presence of TAP-SiO₂@AuNPs (black dots). Reprinted from *Biomaterials*, 150, Kwon SP, Jeon S, Lee SH, et al. Thrombin-activatable fluorescent peptide incorporated gold nanoparticles for dual optical/computed tomography thrombus imaging. 125–136. ©Copyright 2018, with permission from Elsevier. [DOI: 10.1016/j.biomaterials.2017.10.038].⁶²

In order to target the integrin $\alpha\text{v}\beta 3$ receptor and the laminin receptor on B16F10 melanoma cells, respectively, the tripeptide RGD and the pentapeptide YIGSR were affixed to gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) and rhodamine B (RhB). According to the experimental findings, the probes outperformed the traditional Gd-DTPA and both demonstrated low cytotoxicity, quick imaging, and long-lasting effects.⁷³

Through genetic engineering, the RGD-RFP-LBT-Gd molecular probe was created in *E. coli*. Its structure consists of a short LBT peptide that can bind Gd³⁺, a red fluorescent protein, and a tumor-targeting RGD peptide. The stability of the RGD-RFP-LBT-Gd probe is good. Subsequent in vitro and in vivo studies have demonstrated the probe’s strong

Table 3 Summary of Peptide-Based Fluorescent Probes for Multimodal Imaging

Imaging Modality	Probe/Strategy	Peptide Sequence	Target/ Application	Functional Features	Ref.
NIRF + CT	TAP-SiO ₂ @AuNPs	Thrombin substrate peptide	Thrombus detection	Thrombin-activated signal recovery; dual-modal imaging	[62]
NIRF + PET	RGD ₂ -Cy5.5- ⁶⁴ Cu	c(RGDyK) ₂	Integrin $\alpha v \beta 3$	High specificity targeting; intraoperative navigation	[66]
NIRF + PET	⁶⁸ Ga-Glu-urea-Lys-HBED-CC-IRDye800CW	Glu-urea-Lys (Ahx)	PSMA	Precise tumor visualization	[67]
PAI + Enzyme-responsive	ACPP photoacoustic probe	Ceeee[Ahx]	MMP-2	Enzyme-responsive signal activation; tumor microenvironment imaging	[70]
MRI + NIRF	RGD/YIGSR-Gd-DTPA-RhB	RGD, YIGSR	Integrin $\alpha v \beta 3$ / Laminin receptor	Rapid, low-toxicity, and long-lasting dual imaging	[73]
MRI + NIRF	RGD-RFP-LBT-Gd	RGD + LBT motif	Integrin $\alpha v \beta 3$	Strong MRI and fluorescence signal; high tumor targeting	[72]

fluorescent signal for imaging tumor locations, high resolution MRI imaging, low cytotoxicity, high tumor cell uptake, and effective tumor targeting.⁷²

Table 3 Summary of Multimodal Imaging Probes Based on Peptides.

Peptide Fluorescent Probes for the Diagnosis and Treatment of Non-Tumor Diseases Heterotopic Ossification

Heterotopic ossification (HO) is defined as the occurrence of extraskelatal bone in soft tissues⁷⁴ and is commonly seen after joint replacement, spinal cord injury, traumatic brain injury, blast injury, elbow and acetabular fractures, and thermal injury.⁷⁵ Early diagnosis and treatment is important to inhibit the progression of heterotopic ossification.

In order to endocytose chondrocytes and penetrate the cartilage matrix, Wang et al used the enrichment property of type II collagen (Col2a1) during the cartilage formation stage of HO. They created a peptide probe, WL-808, with the peptide sequence of WYRGRL. This probe was linked to the fluorescent dye IR-808 via a linker. According to in vitro tests, the probe demonstrated good specificity and minimal biotoxicity. The probe showed persistent and selective fluorescence in animals in vivo.⁷⁶

The MMP family plays an important role in extracellular matrix (ECM) degradation, and its expression is altered in diseases such as rheumatoid arthritis, chronic obstructive pulmonary disease, and bone formation.^{77–79}

A fluorescent probe targeting MMP-2/9 was developed based on the MMP-targeting peptide M2 (sequence: DOTA-KKAHWGFTLD), with the HWGF motif playing a central role in the peptide's binding to MMP. The probe was double-labeled with IRDye 800CW dye and the radioisotope ⁶⁸Ga. In vivo experiments in mice demonstrated that the probe exhibits excellent stability and specificity, effectively targeting the MMP-9 expression region associated with HO, showing significant potential for clinical application.⁸⁰

Rheumatoid Arthritis

For rheumatoid arthritis (RA), methotrexate (MTX) is the recommended medication.⁸¹ However, its clinical usefulness is limited due to its short residence period at the target site and higher systemic adverse effects.

While carrying the fluorescent dye ICG for imaging, ultrasound-imaging liposomes (iELPs) were modified with a functionalized iRGD peptide (CRGDKGPDC) to enable targeted delivery of MTX. The selective enrichment of iELPs in arthritic joints was greatly improved by the iRGD peptide linkage in a mouse model of RA, increasing medication efficacy and decreasing adverse effects. According to histological analysis, mice's joint tissues treated with iELPs and sonicated had significantly lower levels of inflammatory cell infiltration and angiogenesis.⁸²

Compared to normal, RA patients' synovial tissue contains more DNA fragments linked to apoptosis.⁸³ Histones are transferred to the plasma membrane and liberated from the nucleus during apoptosis.⁸⁴ Additionally, apoptosis-targeting

peptide (ApoPep-1) with the sequence CQRPPR can bind histones on the surface of apoptotic cells with specificity,⁸⁵ A fluorescent imaging probe called Cyclic ApoPep-1 (CApoPep-1) was created by In Seop So et al based on this notion in order to visualize and measure apoptosis in a chronic arthritis model. In in vitro, in vivo, and ex vivo detection, it shows higher sensitivity and specificity and is more stable than linear ApoPep-1.⁸⁶

It has been demonstrated that pathologic diseases including osteoarthritis and rheumatoid arthritis exhibit over-expression of matrix metalloproteinases.⁸⁷ To solve this issue, a diagnostic kit (MMP-D-KIT) was created that immobilizes an MMP-13-specific probe made up of the dye Cy5.5, the bursting agent BHQ-3, and the MMP-13-specific peptide GPLGVRGGKGG, which allows MMP-13 to precisely cleave the peptide link between G and V. There are numerous uses for MMP-D-KIT in detecting MMP in various biological materials due to its excellent sensitivity, linear response, and specificity when compared to other techniques.⁸⁸

Alzheimer's Disease

In the past, imaging methods including MRI, PET, CT, and SPECT were typically used to diagnose Alzheimer's disease (AD) in order to find amyloid plaques.^{89,90} However, these techniques are frequently constrained by their low safety, limited spatial resolution, and time commitment. Therefore, it is particularly crucial to develop more modern, highly sensitive and selective diagnostic probes for the detection of these critical biomarkers.⁹¹

A β_{42} -specific flexible ultrasensitive polyvalent-directed peptide polymer (PDPP) were constructed by linking two A β_{42} -specific peptides to a flexible poly D-lysine hydrobromide (PDL) backbone, which significantly enhanced the sensitivity and specificity for the detection of A β_{42} . The P1 peptide (Ac-FRHMTEQGCGK) was hydrophilic, and the P2 peptide (Ac-IPLPFYNGCGK) was hydrophobic, and both were labeled with fluorescein isothiocyanate (FITC) for enhanced detection. Both peptides were biased to bind the hydrophilic N-terminus and hydrophobic C-terminus of A β_{42} , respectively, and their properties matched the A β_{42} target site, significantly increasing the binding affinity. Compared with the single peptide forms (P1-PDPP or P2-PDPP), PDPP showed an approximately 10^3 to 10^5 -fold enhancement in binding affinity and exhibited low biotoxicity.

In addition, PDPP combined with the ZnO nanoporous system for the detection of A β_{42} in cerebrospinal fluid not only enlarged the detection range, but also significantly reduced the limit of detection (LOD) and improved the sensitivity by about 10^4 times, while enhancing the fluorescence signal intensity. This system shows great potential for application in the early diagnosis of Alzheimer's disease.⁹²

Detection of Thrombophilia

Arterial thrombus plays a key role in acute coronary syndromes and stroke,⁹³ therefore, in vivo techniques for detecting thrombus are of great significance.

Magnetic resonance imaging (MRI) has become one of the most promising non-invasive imaging techniques for detecting and characterizing thrombi in vivo.⁹⁴ EP-2104R is a fibrin-targeted MRI contrast agent composed of a Gd(III) core chelated by DOTA and a fibrin-targeting peptide, which enables selective binding to fibrin within thrombi without competing with fibrinogen or collagen. Its small molecular structure provides excellent thrombus penetration and imaging signal. Additionally, its high affinity and slow clearance contribute to superior performance in MRI detection of both acute and chronic thrombi. Compared to conventional Gd-DTPA, EP-2104R offers enhanced thrombus visualization and is suitable for early thrombus detection and age differentiation.⁹⁵

In another study, novel radiolabeled probes (68Ga-FBP14, 111In-FBP15, and 99mTc-FBP16) were developed on the basis of existing gadolinium-based probes (eg, EP-2104R) and validated in a rat thrombus model.

The results showed that 68Ga-FBP14 and 111In-FBP15 possessed high thrombus target/background ratios and rapid blood clearance properties in PET/SPECT imaging, which could effectively differentiate between thrombus and non-target tissues, and the target specificity was further confirmed by triple isotope validation. However, 99mTc-FBP16 performed poorly due to low target uptake and easy aggregation.⁹⁶

Overall, 68Ga-FBP14 and 111In-FBP15 provide new tools for noninvasive imaging of thrombus and show good potential for clinical translation. The development of these probes provides important support for early diagnosis and precision treatment of cardiovascular diseases.

Table 4 Summary of Peptide-Based Fluorescent Probes for Non-Tumor Disease Diagnosis and Treatment

Disease Type	Probe/Strategy	Peptide Sequence	Target/Function	Key Features	Ref.
Heterotopic Ossification	WL-808	WYRGRLL	Type II Collagen	High specificity, low toxicity, persistent fluorescence	[76]
Heterotopic Ossification	M2-IRDye800CW- ⁶⁸ Ga	KKAHWGFTLD	MMP-2/9	Strong targeting, excellent stability	[80]
Rheumatoid Arthritis	iELPs-iRGD-MTX	CRGDKGPDC	Inflammatory synovium	Targeted drug delivery, anti-inflammatory effect	[82]
Rheumatoid Arthritis	CApoPep-I	CQRPPR (cyclic)	Histones on apoptotic cells	High sensitivity and specificity	[86]
Rheumatoid Arthritis	MMP-D-KIT	GPLGVRGGKGG	MMP-13	High sensitivity, specific MMP detection	[88]
Alzheimer's Disease	PDPP	FRHMTEQGCGK + IPLPFYNGCGK	A β 42	Multivalent, high-affinity binding, low toxicity	[92]
Thrombosis	EP-2104R	Fibrin-binding peptide (not specified)	Fibrin in thrombus	High affinity, deep-tissue MRI imaging	[95]
Thrombosis	FBP14 / FBP15 / FBP16	Based on EP-2104R (not specified)	Fibrin	Radiolabeled, PET/SPECT imaging	[96]

Table 4 Summary of Peptide Fluorescent Probes for Disease Diagnosis (Non-Tumor).

Peptide Fluorescent Probes for Metal Ion Detection

Metal ions such as Hg²⁺, Pb²⁺, Cu²⁺, Cd²⁺, and Zn²⁺ play critical roles in various physiological and pathological processes, and their dysregulation is closely linked to diseases. Copper ions (Cu²⁺) and zinc ions (Zn²⁺) play important roles in various physiological and pathological processes in the human body. Cu²⁺ is involved in angiogenesis and promotes tumor invasion and metastasis. Zn²⁺ is a key factor in enzymatic activity and immune responses, and its homeostatic imbalance has been closely linked to diseases such as Alzheimer's disease and prostate cancer. Mercury ions (Hg²⁺), lead ions (Pb²⁺), and cadmium ions (Cd²⁺) are typical toxic metals whose intake or accumulation poses serious threats to human health. Hg²⁺ and Pb²⁺ exhibit significant neurotoxicity, leading to cognitive impairment and neurodegenerative disorders. Cd²⁺ is closely associated with nephrotoxicity and carcinogenicity, causing lesions in various organs and tissues.^{97–108}

Probes for Biologically Relevant Metal Ions

A fluorescent probe, L, incorporating a targeting peptide (Pro-Gly-His-Trp-NH₂), was developed for the efficient detection of Zn²⁺ ions, demonstrating robust detection performance. Each Zn²⁺ ion was found to coordinate with two probe molecules through two amide groups and two imidazole groups, forming a stable complex. This coordination event induces a proportional fluorescence response via fluorescence resonance energy transfer (FRET), enabling a highly selective and sensitive approach for Zn²⁺ detection.¹⁰⁹

The FLH probe offers an efficient and accurate approach for detecting copper ions (Cu²⁺). Its lysine backbone, along with amino groups in the side chain, not only facilitates the attachment of functional groups but also provides substantial design flexibility. FLH binds to Cu²⁺ through histidine residues located on both termini, exhibiting a distinct fluorescence on/off response, high selectivity, rapid detection capability, and excellent recyclability.¹¹⁰

FGGH (FITC-Gly-Gly-His-NH₂) is a peptide-based fluorescent probe designed for the highly selective detection of Cu²⁺. Its design is inspired by the amino-terminal Cu(II)- and Ni(II)-binding (ATCUN) motif found in metalloproteins, allowing for specific recognition through a square planar coordination involving the amino-terminal nitrogen, two peptide nitrogen atoms, and the imidazole nitrogen. According to the Hard-Soft Acid-Base (HSAB) theory, the imidazole nitrogen in histidine (His) and the nitrogen in glycine (Gly) act as soft bases, while Cu²⁺ is a soft acid, enabling stable binding under physiological conditions. This makes FGGH an efficient sensing platform for Cu²⁺ detection.¹¹¹

Probes for Toxic Metal Ions

Common methods for mercury ion detection include atomic absorption spectrometry (AAS), voltammetry, and chromatography; however, these techniques often suffer from significant interferences and lengthy processing times.¹¹²

In order to overcome these constraints, the fluorescent probe DGRK was created by conjugating a monoacyl fluorophore with the tripeptide Gly-Arg-Lys-NH₂. This probe successfully overcomes the limitations of traditional mercury ion detection techniques in terms of specificity and efficiency thanks to its quick response, high stability, great selectivity, and low biotoxicity. According to experimental findings, Hg²⁺ exhibits a strong binding affinity with DGRK and forms coordination bonds with the tripeptide's amino and amino-nitrogen atoms. These results demonstrate DGRK's potential as a viable option for mercury ion detection.¹¹³

Traditional lead ion detection methods often involve prolonged analysis times and complex sample pretreatment procedures.¹¹⁴ In response to these challenges, recent studies have focused on developing more efficient and convenient detection strategies. A novel ratiometric fluorescent probe has garnered significant attention due to its superior performance. This probe utilizes the peptide moiety Gly-Ser-Met-COOH, in which carboxyl and hydroxyl groups serve as hard ligands and thioether groups as soft ligands, facilitating selective recognition and binding of Pb²⁺. This structural configuration substantially enhances the sensitivity and specificity of lead ion detection, making it a promising tool for practical applications.¹¹⁵

Wang et al designed a fluorescent switching probe, L, for the highly selective detection of Cd²⁺ ions. This probe is constructed using a dansyl fluorophore conjugated to a tetrapeptide (Dansyl-Glu-Pro-Gly-Cys). The Cd²⁺ ion coordinates with the probe through two distinct ligand sites—the oxygen atom of glutamic acid (Glu) and the sulfur atom of cysteine (Cys)—resulting in the formation of a stable coordination complex.¹¹⁶

Table 5 Summary of Peptide Fluorescent Probes for Metal Ion Detection.

Peptide-Coupled Drugs for Targeted Drug Delivery

The conjugation of payloads with targeted ligands enhances the therapeutic index of highly potent or toxic cytotoxic drugs while mitigating the adverse effects associated with their administration.¹¹⁷ Antibody-drug conjugates (ADCs) have emerged as a well-established therapeutic strategy for the selective delivery of cytotoxic agents to tumor sites, improving treatment efficacy and minimizing systemic toxicity.¹¹⁸ peptide-drug conjugates (PDCs) offer an alternative approach with distinct advantages. PDCs are easier to synthesize and allow for structural modifications that facilitate rational drug design, improving bioavailability, affinity, and stability. Additionally, peptides tend to exhibit lower immunogenicity, making them a promising platform for therapeutic development.

Table 5 Summary of Peptide-Based Fluorescent Probes for Metal Ion Detection

Metal Ion Type	Probe/Strategy	Peptide Sequence	Target/Recognition Mechanism	Key Features	Ref.
Zn ²⁺ (Zinc)	Probe L	Pro-Gly-His-Trp-NH ₂	Zn ²⁺ coordinates with two probe molecules via amide and imidazole groups	FRET-based, high selectivity and sensitivity	[109]
Cu ²⁺ (Copper)	FLH	Lysine- and histidine-containing peptide (sequence not fully specified)	Binds Cu ²⁺ via histidines at both termini	Fluorescence on/off switching, fast response, recyclable	[110]
Cu ²⁺ (Copper)	FGGH	FITC-Gly-Gly-His-NH ₂	ATCUN motif: square planar coordination via N-terminal nitrogen, two peptide nitrogens, and histidine imidazole	Metalloprotein mimicry, highly selective	[111]
Hg ²⁺ (Mercury)	DGRK	Gly-Arg-Lys-NH ₂	Coordinates via amino and amino-nitrogen atoms	High specificity, low toxicity, fast response	[113]
Pb ²⁺ (Lead)	Ratiometric probe	Gly-Ser-Met-COOH	Hard ligands (COOH/OH) + soft ligand (thioether) for Pb ²⁺ binding	High sensitivity and specificity, ratiometric signal	[115]
Cd ²⁺ (Cadmium)	Probe L	Dansyl-Glu-Pro-Gly-Cys	Coordinates via Glu oxygen and Cys sulfur atoms	Stable coordination, fluorescence switching	[116]

Lutathera (^{177}Lu -dotatate) is a peptide-drug conjugate (PDC) composed of a somatostatin analog linked to a radionuclide via DOTA. It received FDA approval in January 2018 for the treatment of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that express somatostatin receptors.¹¹⁹

TH1902 is a drug-peptide conjugate composed of docetaxel and the peptide TH19P01 (Ac-GVRAKAGVRN(Nle)FKSESY). It targets the Sortilin 1 (SORT1) receptor and is being developed for the treatment of various advanced solid tumors that are SORT1-positive. Currently, it is in Phase I clinical trials and has been granted Fast Track designation by the FDA. In addition, when TH19P01 is combined with doxorubicin, the resulting drug, TH1904, demonstrates high tolerance and efficacy in the human ovarian ES-2 tumor xenograft mouse model. This study is currently in the preclinical research stage.¹²⁰

^{117}Lu -PSMA-617 is a peptide receptor radionuclide therapy (PRRT) agent, formed by conjugating PSMA-617 with ^{117}Lu -dotatate via a DOTA chelator. PSMA-617 consists of a Glu-urea binding motif and a DOTA chelator, enabling high-affinity binding to prostate-specific membrane antigen (PSMA).¹²¹ Upon binding to PSMA on the cell membrane, Lu-PSMA-617 undergoes internalization, leading to the release of β -particle radiation, which induces DNA damage and subsequent tumor cell death.¹²² The VISION Phase III trial evaluated the efficacy of ^{117}Lu -PSMA-617 in combination with standard therapy for PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). The trial successfully met its primary endpoints, demonstrating significant improvements in overall survival (OS) and progression-free survival (PFS)¹²³

GRN1005 is a peptide-drug conjugate targeting low-density lipoprotein receptor-associated protein-1 (LRP-1), consisting of paclitaxel combined with Angiopep-2, which facilitates blood-brain barrier (BBB) penetration and reach therapeutic concentrations in tumor tissue. Phase I clinical trials demonstrated that GRN1005 was well tolerated in patients with recurrent glioma, with a maximum tolerated dose (MTD) of 650 mg/m² administered every three weeks. The most common toxicities were neutropenia and fatigue, with no central nervous system (CNS) toxicity observed. Pharmacokinetic analysis showed dose-proportional exposure, with some patients exhibiting disease stabilization or remission. GRN1005 is currently undergoing Phase II clinical trials.¹²⁴

Conclusion

Peptide-based fluorescent probes, owing to their small size, excellent biocompatibility, and high targeting specificity, have shown great promise in tumor diagnosis, image-guided surgery, metal ion detection, and targeted drug delivery. By selectively binding to tumor-associated biomarkers and incorporating diverse fluorescence mechanisms, these probes enable real-time, precise visualization of pathological processes, offering significant potential for clinical translation. However, challenges such as enzymatic degradation, short circulation time, and off-target effects still hinder their in vivo stability and imaging accuracy. Future research should focus on enhancing probe stability, prolonging half-life, and developing multifunctional, activatable systems capable of responding to complex disease microenvironments. The continued optimization of peptide design and synthetic strategies will be critical to advancing their clinical utility in precision oncology and beyond.

Acknowledgment

The illustrations in this manuscript were created with the support of Li Dongping using the BioRender platform. Their contribution is gratefully acknowledged.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Natural Science Foundation of Wuhan (Project number: 2024040801020356) and the Hubei Provincial Natural Science Foundation of China (Project number: 2023AFB824).

Disclosure

The authors confirm that there are no financial interests or personal relationships that could have influenced the work presented in this paper. All authors state that they have no relevant financial or personal connections to disclose.

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