# 纳米探针检测帕金森病的研究进展

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**摘要**: 帕金森病 (Parkinson's disease, PD) 为常见的神经退行性疾病, 典型症状为静止性震颤和肌强直等, 可严重降低患者的生活质量。因此早期精准诊断PD对改善患者预后至关重要。传统检测方法存在灵敏度低、有创性等局限, 而纳米探针凭借高特异性、高灵敏度及多模态成像能力, 为PD精准诊断和治疗提供了全新机遇。本文系统综述了近年来纳米探针在PD检测中的研究进展, 重点介绍了纳米探针的分类及功能化策略, 以及其在PD生物标志物检测等方面的应用。同时, 本文也分析了当前面临的生物相容性、临床转化等挑战, 并对其未来发展方向进行了展望, 以期为PD的早期诊断和精准治疗提供新的思路和参考。

**关键词**: 纳米探针; 帕金森病; 疾病检测; 探针设计; 生物成像

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# Research progress on the detection of Parkinson's disease by nanoprobes

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**Abstract**: Parkinson's disease (PD) is a common neurodegenerative disorder, characterized by typical symptoms such as resting tremor and muscle rigidity, which can severely impair patients' quality of life. Therefore, early and accurate diagnosis of PD is crucial for improving patient prognosis. Traditional detection methods have limitations including low sensitivity and invasiveness, whereas nanoprobes, with their high specificity, high sensitivity, and multimodal imaging capabilities, offer new opportunities for precise diagnosis and treatment of PD. This article systematically reviews recent advances in the application of nanoprobes for PD detection, with a focus on the classification and functionalization strategies of nanoprobes, as well as their applications in the detection of PD biomarkers and related fields. Additionally, it analyzes current challenges such as biocompatibility and clinical translation, and provides an outlook on future development directions, aiming to offer new insights and references for the early diagnosis and precise treatment of PD.

**Key words**: nanoprobe; Parkinson's disease; disease detection; probe design; biological imaging

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帕金森病 (Parkinson's disease, PD) 是常见的神经退行性疾病, 主要病理特征为黑质致密部多巴胺能神经元退化、细胞内路易小体的形成、α-突触核蛋白 (α-synuclein, α-Syn) 异常聚集及氧化应激损伤等[1]。随着全球老龄化进程的加速, PD 患者数量正逐年攀升, 目前中国的帕金森病患者超过 300 万人, 位居世界第一[2]。PD 患者的典型症状为静止性震颤、运动迟缓和肌强直等运动障碍, 同时伴随神经精神症状、睡眠障碍等非运动症状, 严重影响其生活质量[3]。

目前临床诊断 PD 主要是依靠对患者临床症状的观察和量表评估, 然而当患者出现明显的运动症状时, 多巴胺能神经元损失往往已较严重, 此时将错过对患者的最佳干预时机[4]。传统分子影像技术如正电子发射断层显像 (positron emission tomography, PET) 和单光子发射计算机断层显像虽然有助于评估多巴胺能系统功能, 但存在辐射暴露、成本高昂等局限性[5]。脑脊液检测虽能提供 α-突触核蛋白等生化数据, 但具有侵入性, 患者接受度低[6]。因此, 开发能够实现早期诊断 PD 的新技术已成为当务之急。

化学探针检测帕金森病具有高灵敏度和分子特异性等优势[5,7,8]。近年来针对帕金森病的检测已开发了许多探针, 例如特异性识别 α-Syn 聚集体的荧光探针 (如基于分子转子荧光团的探针)[9], 以及整合 PET 与光学成像的多模态探针 (如 $^{18}$F 修饰的多模态探针)[5], 能够实现病理蛋白的可视化追踪与多尺度成像。然而传统探针仍存在血脑屏障穿透效率低、靶向性不足及难以区分寡聚体与纤维等局限性。而纳米生物技术的发展为解决这些不足提供了新途径, 纳米探针在生物标志物检测和分子成像等领域展现出较大潜力[10,11]。纳米探针凭借其可功能化表面、尺寸可调性及多重信号放大能力, 显著提升了血脑屏障穿透效率、靶向特异性及诊疗一体化潜力, 为 PD 的早期精准检测提供了理想平台[7,12,13]。综上, 当前 PD 纳米探针在穿透性、靶向性、抗干扰性及安全性方面仍存在诸多技术瓶颈, 其功能化修饰策略与应用场景也有待系统梳理。图 1 直观呈现了 PD 纳米探针开发中的主要问题−改进策略−应用场景, 涵盖了本综述将重点讨论的四大主要痛点、针对性优化方案, 以及探针覆盖的检测靶点与适用样本范围。后续章节将围绕图中各模块展开详细论述, 本文聚焦纳米探针在 PD 检测领域的最新研究成果, 重点通过介绍针对 α-突触核蛋白、神经递质与代谢物、小分子活性物质、单胺氧化酶的检测型纳米探针, 综述近年来该领域的研究进展。

## 1 纳米探针的分类及功能化策略

### 1.1 纳米探针的分类

根据核心材料和功能特性, 纳米探针主要可分为 (表 1) 无机纳米探针、有机纳米探针和混合纳米探针等三大类型[13-15]。其中, 无机纳米探针主要包括贵金属纳米粒子 (如金银纳米颗粒)、量子点 (quantum dots, QDs) (如 CdSe)、磁性纳米粒子 (如 $Fe_3O_4$) 等, 具信号强度高、稳定性好等优势。有机纳米探针则主要包括脂质体、聚合物纳米粒子等, 具有良好的生物相容性和可降解性等优势。混合纳米探针则整合了无机和有机组分的优势, 实现了功能优化和多功能集成。

### 1.2 探针诊断 PD 面临的主要问题

尽管纳米探针在 PD 检测中优势显著, 但仍面临多重核心问题, 制约其诊断性能与临床转化, 具体可归纳为以下方面: ① 血脑屏障 (blood-brain barrier, BBB) 穿

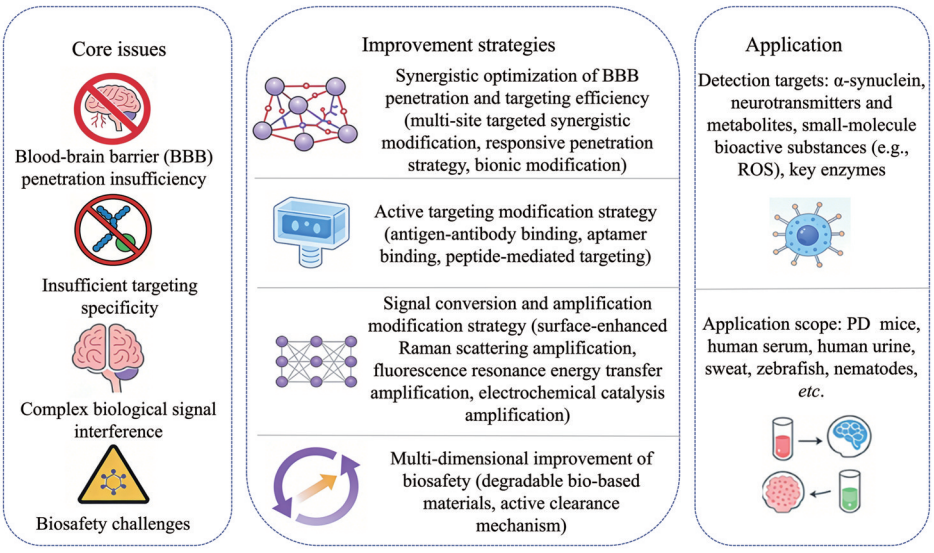



**Figure 1** Schematic diagram of core issues−improvement strategies−application correlation of PD nanoprobes. PD: Parkinson's disease

**Table 1**　Different types of nanoprobes. QDs: Quantum dots; MRI: Magnetic resonance imaging; MOFs: Metal-organic frameworks

| Type | Core material | Functional characteristics | Application |
|---|---|---|---|
| Inorganic nanoprobes | Noble metal nanoparticles (e.g., gold, silver nanoparticles) | Strong surface plasmon resonance effect, excellent light scattering and absorption properties | Surface-enhanced Raman scattering imaging, photoacoustic imaging |
| | QDs (e.g., CdSe) | High fluorescence quantum yield, tunable emission spectrum, good photostability | Fluorescence imaging |
| | Magnetic nanoparticles (e.g., $Fe_3O_4$) | Strong magnetic responsiveness, high $T_2$ relaxivity, stable magnetic properties, easy to achieve magnetic targeting | MRI |
| Organic nanoprobes | Liposomes | Excellent biocompatibility, easy to encapsulate fluorescent dyes or MRI contrast agents, readily surface-modifiable | Multifunctional imaging carrier/platform (for fluorescence imaging, MRI, *etc*.) |
| | Polymer nanoparticles | Excellent biodegradability, controllable structural stability, easy to functionalize, strong capacity for loading fluorescent molecules | Fluorescence imaging |
| | Self-assembled peptides | Good biocompatibility, easy to modify with targeting ligands, capable of forming ordered structures | Building block of multifunctional imaging probes (capable of integrating fluorescent or paramagnetic modules) |
| Mixed nanoprobe | MOFs | High porosity, ability to load fluorescent molecules/magnetic nanoparticles, combining the stability of inorganic materials and the tunability of organic materials | Fluorescence/MRI multimodal imaging |
| | Quantum dot-liposome composites | Combining the excellent fluorescence performance of QDs and the high biocompatibility of liposomes, readily functionalizable | Fluorescence imaging or MRI |
| | Gold-polymer nanoparticles | Combining the local surface plasmon resonance effect of gold nanoparticles and the biodegradability of polymers, capable of simultaneously loading imaging reagents and targeting molecules | Photoacoustic/fluorescence multimodal imaging |

透效率低下[16]: PD病理标志物多富集于脑内, 纳米探针需跨越BBB才能实现靶向检测, 但多数探针因尺寸过大、表面电荷不适配等问题, 脑内递送效率极低, 难以达到有效检测浓度。② 靶向特异性不足[17-19]: $\alpha$-Syn聚集体存在多种构象, 现有靶向配体难以精准区分, 易与正常蛋白非特异性结合产生假阳性; 同时PD伴随的神经炎症会激活小胶质细胞吞噬探针, 进一步降低靶向效率。③ 复杂生物环境中的信号干扰[16,20]: PD患者体液及脑内微环境成分复杂, 蛋白质、还原性物质等可能与探针相互作用, 改变其光学/磁学特性或破坏信号分子结构, 导致信号淬灭、灵敏度下降。④ 生物相容性与长期安全性隐患[21,22]: 部分无机纳米材料本身具细胞毒性, 降解产物可能加剧脑内氧化应激损伤; 探针尺寸、表面基团可能引发免疫反应, 且PD老年患者代谢能力弱, 探针长期滞留易致累积毒性, 相关长期安全性数据匮乏。

### 1.3　纳米探针的功能化策略

纳米探针的功能化策略是突破上述应用难点的核心手段, 通过精准的表面修饰与结构设计, 可实现血脑屏障穿透增强、靶向性提升、信号放大及生物相容性优化等核心目标。结合PD检测的应用需求, 纳米探针功能化策略主要包括: 主动靶向修饰策略、信号转换与放大修饰策略、生物相容性与安全性优化修饰策略三大类。

**1.3.1　主动靶向修饰策略**　核心目标是提升探针对PD病理区域 (如黑质、纹状体) 及特定生物标志物 (如$\alpha$-Syn聚集体、多巴胺转运体) 的识别特异性, 减少非特异性结合, 同时辅助提升血脑屏障穿透效率。其核心原理是通过共价结合或非共价吸附的方式, 将靶向配体修饰于探针表面, 借助配体与靶标分子的特异性相互作用 (如抗原–抗体结合[23]、适配体结合[24]、肽介导靶向[25]等) 实现精准靶向。具体可分为三类: ① 抗体–抗原识别靶向[18,19,26]: 选用针对PD核心生物标志物的特异性抗体作为靶向配体, 如抗$\alpha$-Syn寡聚体抗体、抗多巴胺转运体抗体等。该策略的优势在于亲和力高、特异性强, 能够精准识别PD相关的关键生物标志物, 如寡聚化或错误折叠的$\alpha$-Syn, 为早期PD病理状态的精准判断提供可能。基于抗体的纳米探针在检测脑脊液或外周血中的特异性$\alpha$-Syn构象方面展现出巨大潜力。但该策略存在固有缺陷: 抗体分子质量大, 可能影响纳米探针穿越BBB的效率; 且抗体属于蛋白质, 存在稳定性较差、易变性、生产成本高及潜在的免疫原性等问题, 为其在体内的长期应用带来了挑战。② 适配体结合靶向[27,28]: 适配体是通过体外筛选技术获得的小片段单链DNA或RNA, 可特异性结合$\alpha$-Syn、多巴胺等PD相关靶标。与抗体相比, 适配体具有显著优势: 体积小、易于合成与修饰、稳定性好且免疫原性低。针对$\alpha$-Syn等PD标志物的适配体已被开发, 为构建小型化、高稳定性的纳米探针提供了可能。但其亲和力和特异性有时稍逊一筹, 在复杂的体内环境中, 核酸适配体易被核酸酶降解。③ 肽介导靶向[17,29]: 选用兼具靶向识别与穿透功能的多肽作为配体, 主要包括两类:

一是特异性结合靶标的肽段 (如α-Syn纤维结合肽、多巴胺受体特异性肽); 二是细胞穿膜肽, 可辅助提升血脑屏障穿透效率。该策略的核心优势是分子质量极小 (通常 < 5 kDa)、合成简便、修饰灵活, 可通过靶向肽与穿膜肽的双肽修饰实现穿透−靶向协同。但肽介导靶向的不足在于亲和力普遍低于抗体, 部分肽段在体内易被蛋白酶快速水解, 导致靶向作用时间较短, 需通过环化修饰或与聚合物偶联提升稳定性。

**1.3.2 信号转换与放大修饰策略** 针对PD生物标志物 (如α-Syn寡聚体、多巴胺) 在早期体内浓度极低的特点, 通过功能化修饰构建信号放大机制, 提升探针的检测灵敏度, 突破复杂生物环境中的信号干扰。主流策略包括以下三类: ① 表面增强拉曼散射放大[30]: 核心是将探针核心材料选用贵金属纳米粒 (金、银纳米粒), 并通过表面修饰调控纳米粒聚集状态——当探针与靶标结合后, 纳米粒发生特异性聚集, 形成“热点”区域, 使拉曼信号强度提升。该策略的优势是信号稳定性强、抗干扰能力突出, 可实现单分子级检测; 局限性是需精准调控纳米粒尺寸与修饰密度, 否则易产生非特异性聚集导致信号假阳性。② 荧光共振能量转移放大[31]: 通过修饰供体−受体荧光对 (如荧光素−淬灭剂、量子点−罗丹明) 构建关闭−开启型信号机制: 未结合靶标时, 供体与受体近距离接触, 荧光被淬灭; 结合靶标后, 探针构象改变导致供体与受体分离, 荧光恢复并放大。该策略的优势是特异性强、响应速度快, 可实现实时动态检测; 局限性是在脑内高荧光背景环境中, 可能存在荧光串扰, 需选用近红外荧光对减少背景干扰。③ 电化学催化放大[32]: 主要用于电化学纳米探针的修饰, 通过在探针表面修饰催化活性物质 (如铂纳米簇、氧化石墨烯), 当探针与靶标 (如多巴胺) 结合后, 催化活性物质可加速靶标的氧化还原反应, 产生显著增强的电流信号。该策略的优势是检测速度快、成本低, 适用于体外体液检测; 局限性是体内应用受电极植入限制, 主要用于体外诊断场景。

**1.3.3 生物相容性与安全性优化修饰**[33,34] 通过表面功能化修饰降低探针毒性、减少免疫反应、缩短体内滞留时间, 为临床转化奠定基础。核心修饰策略包括以下三类: ① 亲水性聚合物包裹修饰[35]: 选用生物相容性优异的亲水性聚合物 (如聚乙二醇、聚乳酸−羟基乙酸共聚物) 包裹探针核心材料, 形成致密的亲水层。其核心作用是: 一是降低无机纳米材料 (如量子点、贵金属) 的直接细胞毒性; 二是减少血浆蛋白吸附, 延长血液循环时间; 三是调控探针表面电荷 (趋于中性), 减少对血脑屏障内皮细胞的损伤。但需注意聚合物包裹厚度的调控——过厚包裹会增加探针尺寸, 降低血脑屏障穿透效率。② 生物基材料替代修饰[36]: 选用天然生物材料 (如多糖、蛋白质、细胞膜) 替代合成材料或无机材料作为探针载体, 从源头提升生物相容性。该策略的优势是生物相容性极佳、免疫原性极低; 局限性是部分生物基材料 (如蛋白质) 稳定性较差, 需通过交联修饰提升结构稳定性。③ 主动清除机制修饰[37]: 通过表面修饰特异性配体, 引导探针在完成检测后被体内代谢系统主动清除, 缩短滞留时间。该策略为解决PD老年患者代谢能力弱导致的毒性累积问题提供了有效路径, 但需精准调控配体修饰密度, 避免影响探针的靶向与穿透功能。

## 2 纳米探针检测帕金森病的研究进展

基于帕金森病的病理机制与生物标志物分布特点, 目前开发的PD检测纳米探针已建立起多层次的靶向识别体系: 一方面, 聚焦于PD病理蛋白的探针可特异性结合α-突触核蛋白的寡聚体或纤维状聚集体, 为疾病早期诊断提供关键证据; 另一方面, 面向神经功能失调的探针可动态监测多巴胺、左旋多巴等神经递质与代谢物的水平变化, 其浓度波动与PD运动症状严重程度密切相关。此外, 还包括可响应病理微环境变化的活性物质探针 (如活性氧等), 用于评估PD过程中的氧化应激状态; 及针对单胺氧化酶等关键代谢酶的探针, 其活性异常会促进多巴胺分解、加剧神经损害。这些面向不同靶标的纳米探针, 在检测限、特异性及体内外应用适应性方面各具特点 (表2[10,11,16,20,36,38-60]), 为后续探针结构设计、性能优化及临床应用策略提供了参考。

### 2.1 靶向α-突触核蛋白的纳米探针

α-Syn的错误折叠和异常聚集是PD的核心病理特征之一, 发展高灵敏、高特异性检测其聚集态的方法对PD的早期诊断具有关键意义。近年来, 多种功能纳米探针被开发用于α-Syn的检测, 显著提升了检测性能并拓展了应用场景。2020年Zhang等[38]构建SWCN伏安传感器, α-Syn检测限达10 amol·L$^{-1}$ (较传统提升1 000倍), 并提升检测特异性与重现性。针对临床诊断中有创取样的痛点, 2022年Miao等[39]开发口服递送的Tb-发光金属有机框架探针 (Tb-MOF@Pt-Aptamer), 实现粪便α-Syn的无创检测, 48 h体内结构稳定、无明显毒性, 检测限0.04 pg·mL$^{-1}$ (S/N = 3), 为无创诊断提供新途径 (图2A)。近年来α-Syn纳米探针的研发进一步向多模态成像与诊疗一体化拓展。2024年Chen等[16]开发可切换T1-T2信号的MRI探针ASOSN, 该探针搭载高度灵敏的反铁磁性纳米颗粒并经单链可变抗体修饰, 能够特异性识别α-Syn寡聚体并有效区分神经炎症背景, 实现了PD早期精准诊断 (图2B)。同年,

**Table 2**　Performance summary of nanoprobes for PD detection. DA: Dopamine; NE: Norepinephrine; EP: Epinephrine; *L*-DOPA: Levodopa; MAO-B: Monoamine oxidase B; MMP3: Matrix metalloproteinase 3; SSAO: Semicarbazide-sensitive amine oxidase; NA: Not available; a pg·mL$^{-1}$

| Probe | Target | Core material | Limit of detection /nmol·L$^{-1}$ | Application scope | Ref. |
|---|---|---|---|---|---|
| SWCN | *α*-Syn | Mixed nanoprobe | $1.00\times10^{-5}$ | Human serum | [38] |
| Tb-MOF@Pt-Aptamer | *α*-Syn | MOFs | 0.04[a] | PD mice | [39] |
| ASOSN | *α*-Syn | Magnetic nanoparticle | NA | PD mice | [16] |
| NR-CDs | *α*-Syn | Nile Red carbon dots | NA | NL5901 nematode | [40] |
| NB-12 | *α*-Syn | Carbon dots | 9.50 | A537 mouse, NL5901 nematode | [10] |
| PX30 | *α*-Syn | Nanobody-modified polydiacetylene | NA | Zebrafish | [11] |
| AgNPs | Multiple catecholamines | Silver nanoprobe | 92.00 (DA), 93.00 (NE), 97.00 (EP) | Aqueous solution | [41] |
| Y-CDs, G-CDs, B-CDs | Multiple catecholamines | Multicolor carbon nanodots | 32.00 (EP), 44.00 (NE), 149.00 (*L*-DOPA) | Human serum | [42] |
| Dop-imprinted MNPs | Catecholamine | Magnetic nanoparticle | 270.00 | Human urine | [43] |
| CuNCs@TA, CuNCs@AA, CuNCs@PMAA | Catecholamine | Copper nanoprobe | 1.00 | Aqueous solution | [44] |
| Mn:ZnS/BSA QDs | DA | Quantum dots | 2.02 | Human serum, human urine | [45] |
| Eu-*α*CD | DA | MOFs | 0.65 | Human urine | [46] |
| AgNPs | DA | Silver nanoprobe | 4.28 | Human body fluid | [47] |
| N-CQDs | DA | Quantum dots | $1.68\times10^{5}$ | Rabbit serum | [48] |
| ZGC/ZIF-8-$NH_2$ | DA | MOFs | 75.00 | Urine, sweat | [49] |
| NGOZC | *L*-DOPA | Graphene oxide quantum dots | 1.78 | *L*-DOPA test solution | [50] |
| $Fe^{2+}$@cys@CuNC | *L*-DOPA | Copper nanoprobe | 6.57 | Human serum | [51] |
| NPCDs | *L*-DOPA | Novel biomass (annona plant) carbon dots | $5.00\times10^{4}$ | Fetal bovine serum | [36] |
| CdTe QDs | *L*-DOPA | Quantum dots | 18.30 | Plasma | [52] |
| NSGQDs | Tyrosine | Graphene quantum dots | 4.20 (PBS), 7.00 (human serum) | Human serum | [53] |
| Eu-MOF | Tryptophan, $Cu^{2+}$ | MOFs | 220.00 (Tryptophan), 90.00 ($Cu^{2+}$) | Aqueous solution | [54] |
| PEP-Au | Tryptophan | Gold nanoparticle | 100.00 | Porcine serum | [55] |
| TAT-Polyp-QL | $H_2O_2$, $Fe^{3+}$ | Organic nanoprobe | 383.20 | PD mice | [56] |
| ZnNPs-H | ROS | Zinc oxide nanoparticle | NA | N2a cell | [57] |
| HV-PEG-RVG29 | $H_2O_2$, viscosity | Peptide bifunctionalized modified carrier-free nanoprobe | NA | PD mice | [20] |
| NIR-MNP | MAO-B | Phospholipid-PEG nanomicelle | NA | PD mice | [58] |
| UCNP/AIEgens | MMP3 | Mixed nanoprobe | 0.12 | PD mice | [59] |
| AuNPs@MEA | SSAO | Gold nanoparticle | 252.00[a] | Human serum | [60] |

Li等[40]则聚焦检测−干预协同, 设计尼罗红衍生的碳点探针 (Nile red based carbon dots, NR-CDs), 可在体外与体内环境中荧光检测*α*-Syn原纤维并抑制其聚集, 兼具诊断与潜在治疗功能 (图2C)。在此基础上, 该团队[10]于2025年进一步优化碳点设计, 开发具溶剂致变色特性的红色荧光碳点 (NB-12), 对*α*-Syn的检测限可低至9.5 nmol·L$^{-1}$, 实现了A53T小鼠和线虫脑切片的*α*-Syn成像。同年Zhao等[11]则另辟蹊径, 开发了一种纳米抗体修饰的聚乙二炔探针 (PX30), 不仅能在活斑马鱼体内实现*α*-Syn淀粉样变性的高信噪比实时拉曼成像, 还能有效抑制*α*-Syn淀粉样变性及清除病理性活性氧, 减轻淀粉样变性对斑马鱼胚胎造成的损害 (图2D)。这些研究不仅推动了*α*-Syn检测技术的灵敏与特异双提升, 也逐步融合诊断与治疗功能, 为PD的早期干预与精准诊疗提供了有力工具。

### 2.2　基于神经递质与代谢物检测的纳米探针

儿茶酚胺水平的异常与多种疾病密切相关, 包括帕金森病、高血压和嗜铬细胞瘤等, 是其潜在生物标志物[61-63]。然而, 由于多巴胺 (dopamine, DA)、去甲肾上腺素 (norepinephrine, NE) 和肾上腺素 (epinephrine, EP) 等儿茶酚胺类物质在结构上高度相似, 传统分析方法难以实现对其精准、快速区分与检测。近年来, 纳米传感技术的发展为这一挑战提供了新的解决途径。2022年Li等[43]开发Dop-imprinted MNPs磁性纳米材料, 借助印迹技术实现人尿液中儿茶酚胺痕量检测, 但未解决结构区分问题。2023年Yin等[44]构建了基于

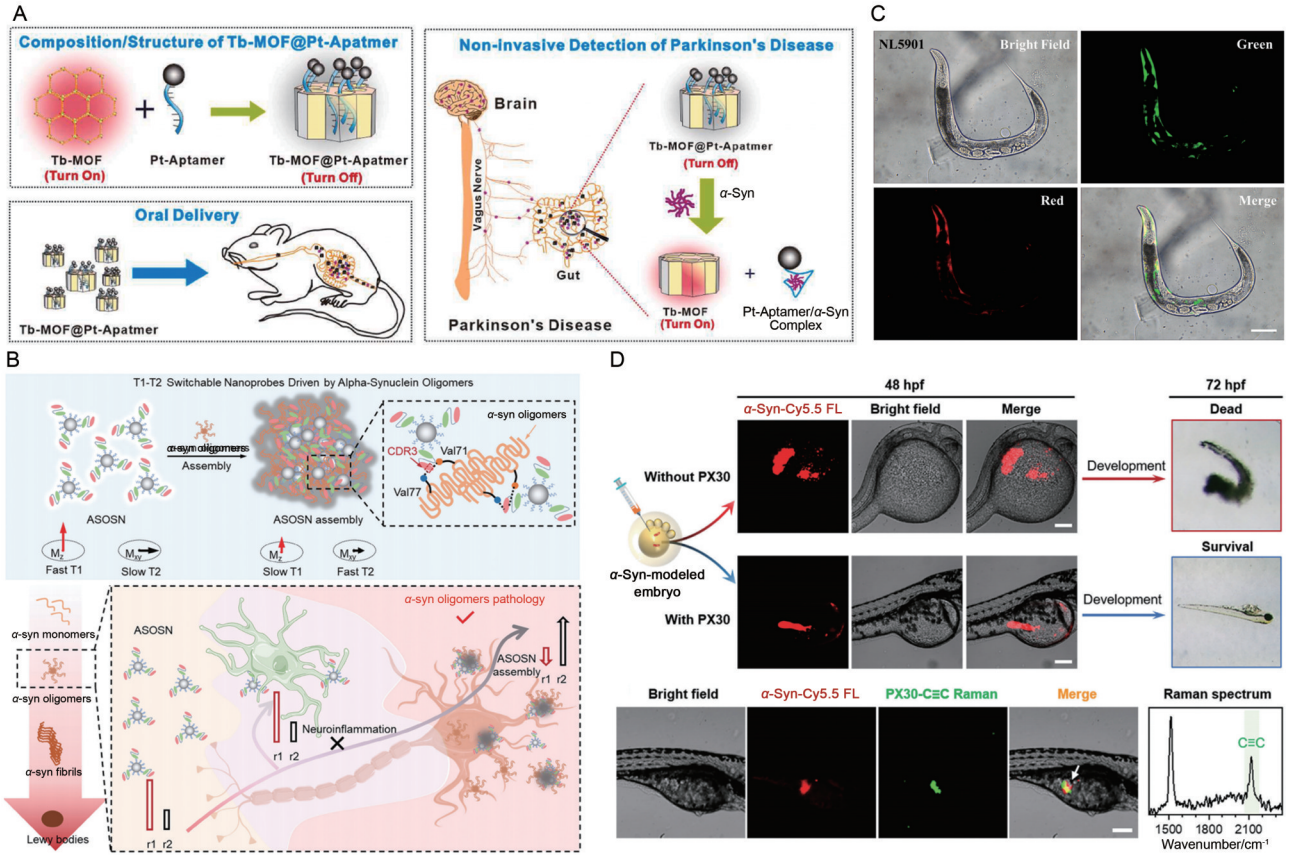



**Figure 2** PD nanoprobes targeting *α*-Syn. A: Schematic of the non-invasive PD monitoring system and its working principle based on the Tb-luminescent metal-organic framework probe (Tb-MOF@Pt-Apt). Adapted from Ref. 39 with permission. Copyright © 2022 Elsevier; B: Schematic illustration of the principle of the T1-T2 switchable MRI probe ASOSN driven by *α*-Syn oligomers. Adapted from Ref. 16 with permission. Copyright © 2024 Wiley; C: Fluorescence images of NL5901 nematodes labeled with probe (NR-CDs). Scale bar = 100 μm. Adapted from Ref. 40 with permission. Copyright © 2024 Elsevier; D: Upper panel: Representative developmental images of *α*-Syn-mimicking embryos treated with and without probe PX30. Lower panel: Interaction between *α*-Syn-Cy5.5 and PX30 in 96 h early larvae, monitored by fluorescence imaging and Raman imaging. Scale bar = 200 μm. Adapted from Ref. 11 with permission. Copyright © 2025 Wiley. NR-CDs: Nile red based carbon dots

铜纳米晶体 (CuNCs) 的新型比色传感器阵列, 成功区分多种结构相似儿茶酚胺, 检测限低至 $10^{-8}$ 至 $10^{-9}$ 摩尔/升。2025 年相关研究进一步升级, Singh 等[41]开发了银纳米比色探针 AgNPs, 可在水溶液中选择性、灵敏性地实时检测 DA、NE 和 EP, 其检测限分别为: DA 为 92 nmol·L$^{-1}$、NE 为 93 nmol·L$^{-1}$、EP 为 97 nmol·L$^{-1}$ (图 3A)。同年, 针对比色探针在多组分同时精准区分与临床现场应用上的不足, Zhang 等[42]进一步提出“多色碳纳米点和便携智能平台”的方案: 通过多色碳纳米点 (Y-CDs/G-CDs/B-CDs) 结合便携智能平台, 实现人血清中儿茶酚胺的可视化区分与定量, 检测限 32.08 至 149.44 nmol·L$^{-1}$, 适配临床现场应用。

多巴胺作为关键儿茶酚胺神经递质, 其浓度异常与帕金森病的发生和发展密切相关。2020 年 Abha 等[45]开发锰掺杂硫化锌量子点 (Mn: ZnS/BSA QDs), 随 DA 浓度增加发光线性下降, 检测限 2.02 nmol·L$^{-1}$, 适配人血清/尿液直接检测。2022 年 Xie 等[46]进一步聚焦临床现场检测需求, 开发了一种高选择性无标记镧系金属有机框架 Eu-*α*CD, 用于检测 PD 患者尿液中的 DA, 在 $10^{-9}$ 至 $10^{-4}$ mol·L$^{-1}$ 浓度范围内响应良好, 检测限为 0.65 nmol·L$^{-1}$, 为临床中对 DA 的可视化和现场检测提供了有效策略 (图 3B)。2024 年 DA 检测呈现多模态与绿色制备趋势, Park 等[47]采用表面声波诱导银纳米粒子 (AgNPs) 聚集的表面增强拉曼散射活性传感技术, 检测限为 4.28 nmol·L$^{-1}$ ($R^2$ = 0.99); Han 等[48]以废果皮制备碳量子点 N-CQDs 荧光探针, 检测限为 0.168 mmol·L$^{-1}$, 兔血清回收率为 98% 至 103%; Pan 等[49]开发非侵入性荧光可视化探针 (ZGC/ZIF-8-$NH_2$), 实现尿液和汗液中 DA 的无创实时检测, 检测限为 0.075 μmol·L$^{-1}$, 无需复杂预处理, 适配 PD 患者长期动态监测。

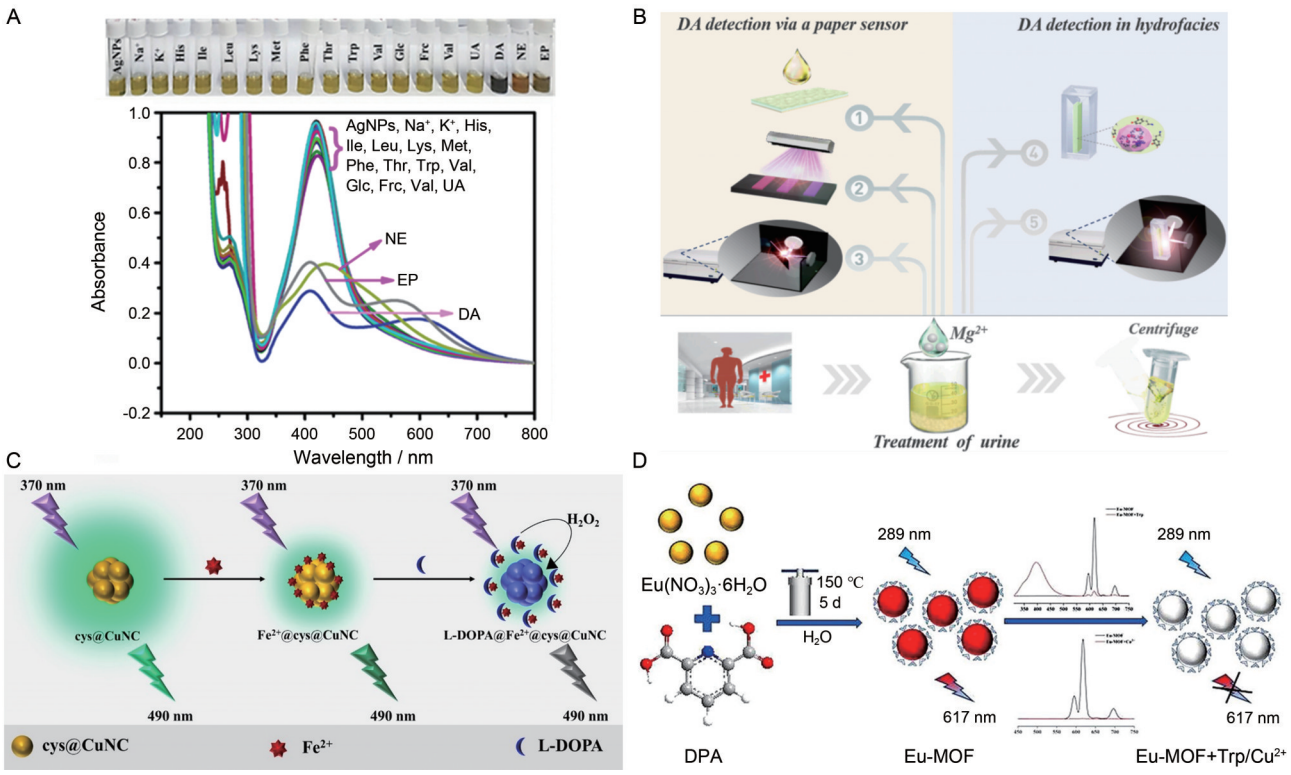



**Figure 3**　PD nanoprobes based on the detection of neurotransmitters and metabolites. A: UV-visible spectra of AgNPs in the presence of interfering substances such as DA, NE and EP. Adapted from Ref. 41 with permission. Copyright © 2025 Royal Society of Chemistry; B: Flow chart for the treatment of patient urine and DA detection process using Eu-*α*CD nanoprobes. Adapted from Ref. 46 with permission. Copyright © 2022 Elsevier; C: Schematic diagram for the detection of levodopa using $Fe^{2+}$@cys@CuNC nanoprobes. Adapted from Ref. 51 with permission. Copyright © 2024 Wiley; D: Schematic diagram of the synthesis of Eu-MOF and its application in the detection of tryptophan and $Cu^{2+}$. Adapted from Ref. 54 with permission. Copyright © 2025 Springer

左旋多巴 (levodopa, *L*-DOPA) 作为帕金森病治疗中最常用的多巴胺前体药物, 其血药浓度监测对疗效评估与不良反应控制至关重要。高剂量使用常引起运动障碍和精神症状等不良反应[64,65], 因此发展高选择性、实时检测方法尤为迫切。2019 年 Moslehipour 等[52]开发 CdTe QDs 比率型探针, 选择性优异, 可在血浆中依次检测 *L*-DOPA。与 Moslehipour 等[52]侧重选择性与复杂体液适用性不同, Biswas 等[50]则更聚焦检测灵敏度的突破, 以满足低浓度 *L*-DOPA 的精准定量需求。2024 年 Biswas 等[50]推出氮掺杂氧化石墨烯量子点纳米材料 NGOZC, 检测限低至 1.78 nmol·$L^{-1}$, 突破灵敏度瓶颈。同年, Varghese 等[51]创新开发双信号响应探针, 用 $Fe^{2+}$ 淬灭的半胱氨酸稳定的铜纳米团簇 ($Fe^{2+}$@cys@CuNC), 作为荧光和比色探针用于检测 *L*-DOPA。其在 0.06～1.31 mmol·$L^{-1}$ 的线性范围内, 检出限为 6.57 nmol·$L^{-1}$, 回收率为 85.75%～115.07%, 既通过双信号交叉验证提升了准确性, 又为不同检测场景 (荧光定量/比色半定量) 提供了灵活性 (图 3C)。2025 年 Huang 等[36]利用番荔枝属植物制备 NPCDs 生物质碳点, 检测限 0.05 mmol·$L^{-1}$, 细胞毒性更低, 为体内 *L*-DOPA 血药浓度实时成像探针研发奠定基础。

PD 的病理进程还伴随酪氨酸 (tyrosine, Tyr)、色氨酸 (tryptophan, Trp) 的代谢紊乱[66]与铜离子 ($Cu^{2+}$) 失衡[67], 这类标志物的检测为 PD 多维度评估提供了补充。2024 年 Anh 等[53]开发 N, S 共掺杂石墨烯量子点探针 NSGQDs, 实现人血清中 3-硝基-*L*-酪氨酸超灵敏检测 (PBS 中检测限 4.2 nmol·$L^{-1}$, 稀释人血清中 7 nmol·$L^{-1}$), 兼具宽检测范围与临床样本适配性。同年, Wang 等[55]构建 PEP-Au 比色传感器, 通过肽适配体–金纳米粒子偶联快速检测 *L*-色氨酸, 线性范围 1 至 1 000 μmol·$L^{-1}$, 反应时间仅 10 s, 提升检测效率。前两项研究均针对单一代谢标志物开发检测工具, 而 Gong 等[54]则进一步突破单分析物检测的局限, 聚焦 PD 中色氨酸代谢紊乱与 $Cu^{2+}$ 失衡的协同监测需求。2025 年 Gong 等[54]聚焦多分析物同步检测, 开发了基于铕的金属有机框架 (Eu-MOF) 的荧光传感探针, 可在中性水溶液 (pH = 7.4) 中同时检测色氨酸和 $Cu^{2+}$, 其检测限分别为 0.22 和 0.09 μmol·$L^{-1}$, 展现出良好的多分析物同步检测能

力 (图3D)。

### 2.3 基于小分子活性物质检测的纳米探针

小分子活性物质通过氧化应激损伤 (如ROS清除) 等, 在帕金森病的病理机制中起核心作用, 并为PD的早期诊断提供关键分子靶点[68]。2022年Yang等[56]开发TAT-Polyp-QL荧光探针, 可高灵敏检测铁离子与ROS双重标志物, 通过荧光颜色转换实现PD精准诊断。2024年Prasad等[57]推出ZnNPs-H氧化锌纳米颗粒, 凭借超氧化物歧化酶纳米酶活性清除过量ROS、修复神经元损伤, 聚焦PD治疗干预。在诊断与单一治疗研究的基础上, Zhang课题组进一步实现了诊疗一体化的突破。2025年Guo等[20]构建了脑靶向无载体纳米探针HV-PEG-RVG29, 该探针不仅能够穿透血脑屏障, 还能在$H_2O_2$和黏度的双刺激下原位产生近红外荧光和光声信号, 用于帕金森病的诊断和治疗 (图4A)。在小鼠PD模型中, 实现了脑部的原位近红外荧光/光声成像, 减轻了多巴胺神经元的损失, 并有效改善了PD小鼠的行为缺陷, 为神经退行性疾病的一体化诊断和治疗开辟了途径。

### 2.4 靶向关键酶的纳米探针

在PD的病理进程中, 多种酶的活性异常与疾病发生发展密切相关, 这些酶不仅是PD病理机制的关键参与者, 也成为PD诊断与干预的重要靶点。例如, 单胺氧化酶B (monoamine oxidase B, MAO-B) 的活性增加会导致中脑黑质致密部区域多巴胺水平降低, 这与PD样表现的发病机制密切相关[69]。此外, 调控神经炎症的基质金属蛋白酶3 (matrix metalloproteinase 3, MMP3)[59]、参与氧化应激的半胱氨酰敏感型胺氧化酶 (semicarbazide-sensitive amine oxidase, SSAO)[60]等, 也相继被证实与PD病理相关。近年来, 科研人员针对这些PD相关酶, 开发了多款高特异性纳米探针。

2023年Zhang等[58]报道了一种可激活的频率上转换发光MAO-B纳米探针 (NIR-MNP), 能够实现在生物样品中高度特异性和实时的MAO-B成像 (图4B)。他们利用NIR-MNP探针, 通过体内生物成像证实了MAO-B抑制剂在小鼠PD模型中延缓PD进展的作用。与Zhang等聚焦MAO-B不同, Li等[59]则将目光投向MMP3, MMP3作为加剧PD神经损伤的关键酶, 其活性升高会促进炎症因子释放, 进一步损伤多巴胺能神经元, 因此同时实现MMP3检测与炎症干预具有重要意义。2021年Li等[59]基于上转换纳米颗粒UCNP/聚集诱导发光分子设计了多功能纳米探针, 不仅能有效检测炎症状态下儿茶酚胺能SH-SY5Y细胞中的MMP3的活性, 同时可抑制MMP3诱导的炎症神经反应, 突破了单一检测型探针的局限, 为PD早期诊断与病理干预的协同提供了新思路。除了MAO-B和MMP3, 半胱氨酰敏感型胺氧化酶 (SSAO) 作为另一种PD潜在生物标志物, 其检测需求更侧重临床转化适用性。SSAO的活性异常与PD患者脑部氧化应激增强、多巴胺能神经元退变密切相关, 而临床诊断需要探针具备高特异性、高灵敏度且经济便捷的特点。2025年Zhao等[60]报道了基于光学金纳米粒子的SSAO活性检测纳米探针AuNPs@MEA, 能通过SSAO特异性氧化反应实现检测, 不仅能在体外PD模型中灵敏识别SSAO活性变化, 还能直接对临床人类血清样本进行实际分析。相比前两款探针更侧重基础研究场景, AuNPs@MEA在检测成本与临床样本适配性上更具优势, 为PD临床诊断的落地提供了可能。

## 3 纳米探针检测PD的核心挑战与现有策略的局限性分析

尽管纳米探针在PD诊断中展现出巨大潜力, 当前其研究仍存在核心挑战: ① 血脑屏障穿透问题[16,70-72], 前文提及的肽介导靶向、抗体/适配体修饰等功能化策略, 虽理论上可通过受体介导内吞等机制提升穿透效率, 但实际应用仍存显著局限: 一是修饰效率与穿透效果难以平衡, 如细胞穿膜肽过量修饰易致探针电荷失衡、被快速清除, 抗体修饰则可能增大探针尺寸超出BBB穿透临界值; 二是PD病理状态下BBB存在异质

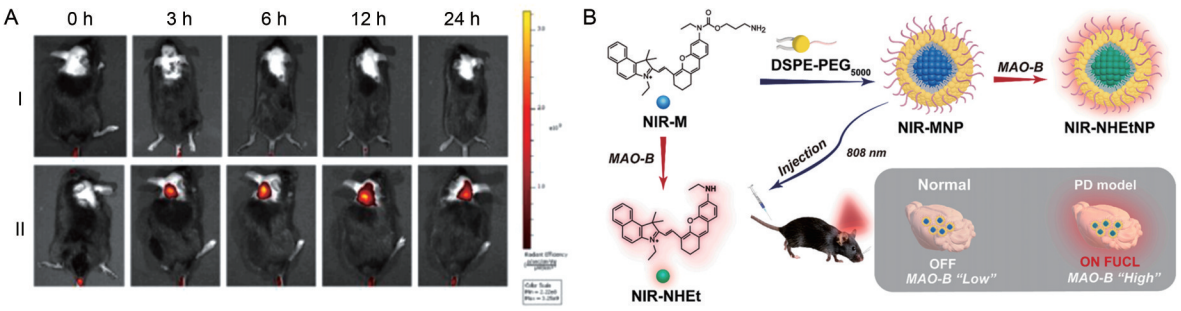



**Figure 4** PD nanoprobes based on the detection of small-molecule bioactive substances and enzymes. A: Fluorescence imaging of HV-PEG-RVG29 nanoprobes in PD mice. Adapted from Ref. 20 with permission. Copyright © 2025 Elsevier; B: Schematic diagram of bioimaging of MAO-B using NIR-MNP nanoprobes. Adapted from Ref. 58 with permission. Copyright © 2023 Elsevier

性, 神经炎症导致的屏障结构重构使同一策略在不同病程患者中效果差异大, 而现有研究多基于标准化动物模型, 难以模拟临床复杂状态; 三是穿透后靶向富集不足, 部分探针虽能少量穿透BBB, 但对黑质、纹状体等核心区域缺乏精准靶向, 脑内有效检测浓度不足, 现有策略仅解决穿透可能性, 未满足高效精准穿透与富集的临床需求。② 生物安全性问题[73], 虽然大多数研究报道的纳米探针在短期内表现出良好的生物相容性, 但其长期安全性仍需系统评估。而在PD的诊断与成像应用中, 其安全性挑战不仅源于纳米材料本身的通用性质, 更与PD特有的病理生理环境密切相关。① 绝大多数系统给药的纳米探针会被BBB阻挡, 导致其递送效率低, 为了增强穿透性而采用的策略 (如增大表面正电荷以促进吸附介导的穿胞作用或使用细胞穿膜肽) 往往会存在一定生物安全性问题[21,22]。并且PD患者的BBB完整性存在争议, 可能在某些脑区出现渗漏或功能障碍, 使得纳米探针的全身暴露风险增加[74,75]。② 纳米探针进入脑实质后, 其与PD特有病理蛋白的潜在相互作用, 可能会带来神经毒性。纳米材料表面 (特别是带有正电荷或疏水表面的材料) 可能作为“种子”或模板, 加速神经元内α-Syn的异常聚集[76]。未能被及时清除的纳米探针可能被小胶质细胞吞噬, 激活NLRP3炎症小体等通路, 诱发神经炎症, 进而加剧多巴胺能神经元的损伤[77]。③ 尺寸较大或表面性质不佳的探针可能长期滞留于脑内, 其长期降解产物 (如金属离子、持久性聚合物) 可能对已经处于应激状态的神经元造成累积性毒性[78]。④ 缺乏大规模临床样本验证[79], 现有研究多基于小样本或动物模型。

## 4　总结与展望

面对上述挑战, 纳米探针在PD诊断中的应用研究正朝着多个方向深入发展: ① BBB穿透与靶向效率的深度协同优化。针对BBB穿透不足、穿透后靶向富集效率低的核心难题, 一方面多靶点协同修饰与响应型穿透策略[80], 平衡穿透效率、靶向性与生物稳定性; 另一方面引入仿生纳米探针[12], 通过仿生修饰 (如脑微血管内皮细胞膜伪装) 增强纳米探针的血脑屏障穿透能力, 并减少免疫清除, 提高靶向递送效率。② 生物安全性多维度提升[36,37]。针对纳米材料毒性累积、长期安全性数据匮乏的问题, 优先采用可降解生物基材料, 引入主动清除机制缩短体内滞留时间, 并完善长期毒性评估数据。③ 非侵入性液体活检技术[81]。针对现有研究多基于动物模型、临床样本验证不足的转化难题, 开发高灵敏度纳米探针用于检测血液、脑脊液甚至唾液中的PD相关生物标志物 (如外泌体α-突触核蛋白、神经丝轻链等), 结合微流控芯片技术, 有望为PD的早期筛查、分期和进展监测提供非侵入性解决方案。④ 人工智能与纳米技术融合[82]。针对传统探针设计效率低、结构优化盲目性大的问题, 通过人工智能辅助纳米探针设计, 能高效筛选靶向分子、优化探针结构并预测其与生物标志物的相互作用, 大幅提升开发效率与成功率。⑤ 多功能与诊疗一体化[83]。诊疗一体化并非直接解决BBB穿透或生物安全性的基础难题, 而是在上述核心问题得到有效缓解后的高阶协同应用方向。更加注重诊断与治疗的协同, 通过设计刺激响应型 (如pH、酶、ROS响应) 纳米探针, 实现病理环境触发下的精准药物释放与实时疗效监测。

纳米探针为帕金森病的精准检测带来了革命性突破, 在材料设计、靶向策略和成像技术等方面取得了显著进展。当前研究已开发出多种基于不同原理的纳米探针, 实现了对α-突触核蛋白、多巴胺、左旋多巴等关键生物标志物的高灵敏度检测与成像。然而, 纳米探针在临床转化过程中仍面临血脑屏障穿透率的精准调控、生物安全性的长期保障等挑战, 后续可通过多靶点修饰、响应型设计、生物基材料应用等技术创新, 探索攻克核心难题。未来随着人工智能辅助设计、诊疗一体化平台构建和多学科交叉融合的深入, 将推动纳米探针技术的临床转化, 在帕金森病的早期诊断、病程监测和个性化治疗中发挥越来越重要的作用, 为改善PD患者预后和生活质量做出重要贡献。

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