中国激光

近红外二区荧光金纳米团簇用于生物医学光子学：进展与挑战

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摘要 近红外二区(NIR-Ⅱ)金纳米团簇(Au NCs)具有明亮的多色荧光、良好的生物相容性和可肾脏清除的特性，已成为当前生物医学光子学领域中备受关注的纳米材料。首先介绍了NIR-Ⅱ Au NCs的合成方法，讨论了其面临的低产率和缺乏规模化制备的问题。其次，介绍了NIR-Ⅱ Au NCs的表面调控技术，讨论了调控团簇表面结构、组成和形态的方法，以及增大发光波长和提高荧光量子产率的方法。然后，总结了NIR-Ⅱ Au NCs在血管成像、淋巴管和淋巴结成像、肿瘤成像以及成像引导治疗等方面的最新研究进展。最后，讨论了NIR-Ⅱ Au NCs在生物医学光子学领域中面临的机遇与挑战。

关键词 生物光学；金纳米团簇；近红外二区荧光；生物医学光子学；生物成像；成像引导治疗

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1 引 言

近年来，近红外二区(NIR-Ⅱ，1000～1700 nm)荧光成像备受关注[1-3]。相较于可见光(300～550 nm)和近红外一区荧光(600～950 nm)，NIR-Ⅱ荧光具有高组织穿透(厘米级)、高分辨(纳米级)、低背景的独特优势。自戴宏杰课题组首次报道碳纳米管材料可用于NIR-Ⅱ荧光活体成像以来[4]，已有量子点[5-6]、镧系掺杂纳米颗粒[7-8]、共轭聚合物纳米颗粒[9]、聚集诱导发光纳米颗粒[10]、有机小分子染料[11]、碳点[12]、金纳米团簇(Au NCs)[13]等材料被开发出来，用于细胞、血管、器官、全身组织的跨尺度、高灵敏、高时空分辨的NIR-Ⅱ荧光成像。这种先进的生物医学光子学成像方法和技术为重大疾病的诊疗研究提供了新工具。

2019年，研究人员使用美国食品药品监督管理局批准的吲哚菁绿(ICG)作为荧光探针，首次实现了肝癌患者微小病灶和转移灶的高灵敏在体NIR-Ⅱ荧光成像，提高了手术切除的精准性[14]。这一研究成果推动了NIR-Ⅱ荧光成像技术的临床转化。但是，由于材料合成的复杂性、体内潜在毒性和临床监管的严格性等问题，能够用于临床研究的NIR-Ⅱ荧光探针非常有限。相较于碳纳米管、量子点、镧系掺杂纳米颗粒等无机纳米材料而言，NIR-Ⅱ荧光金纳米团簇(后文简称为NIR-Ⅱ Au NCs)是一类具有巨大临床转化潜力的候选纳米材料。NIR-Ⅱ Au NCs具有组分单一、性能稳定、尺寸(<3 nm)小以及可肾脏清除的独特优势。近年来，NIR-Ⅱ Au NCs已在肿瘤、心脑血管疾病、细菌感染、脑科学、可植入医疗器械等多个领域中得到成功应用，在重大疾病标志物的高灵敏、高分辨、大深度活体分子成像领域中展现出巨大的应用潜力和良好的临床转化前景。本文主要综述了NIR-Ⅱ Au NCs近5年的研究成果，详细介绍了NIR-Ⅱ Au NCs的合成方法、表面修饰技术和生物医学应用，讨论了NIR-Ⅱ Au NCs在基础研究和临床转化研究中面临的主要挑战，并展望了NIR-Ⅱ Au NCs纳米探针在生物医学光子学领域中的应用前景。

2 NIR-Ⅱ Au NCs的合成

NIR-Ⅱ Au NCs通常以金离子、还原剂和小分子配体为原料，通过化学还原反应生成。其中金离子的浓度、金离子与配体分子的比例及还原剂的种类会直接影响制备的NIR-Ⅱ Au NCs的尺寸和发光波长。目

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前，已建立的水相化学还原法能够在24 h内获得NIR-Ⅱ荧光发光波长（1000～1300 nm）可调谐、具有良好的水溶性和稳定性、表面活性基团丰富的NIR-Ⅱ Au NCs。如图1(a)所示，张晓东课题组采用氯金酸、还原型谷胱甘肽（氯金酸与还原性谷胱甘肽的物质的量之比为2∶3）、弱还原剂一氧化碳为反应物，在室温条件下一步合成了NIR-Ⅱ Au_{25} NCs[13]，其发光波长范围为1100～1350 nm。如图1(d)所示，谢建平课题组使用强还原剂硼氢化钠（$NaBH_4$）在室温条件下制备了NIR-Ⅱ $Au_{44}MBA_{26}$纳米团簇（MBA表示4-巯基苯甲酸，氯金酸与MBA的物质的量之比为1∶2）[15]。其NIR-Ⅱ荧光中心的发光波长分别位于1080 nm和1280 nm。此外，最新的研究结果显示，通过与工程化技术的结合，Au NCs已经可以实现全自动的机器合成，为NIR-Ⅱ Au NCs的质量控制和临床转化奠定了基础。除了可以通过控制Au NCs的尺寸调控其发光波长外，还可用离子掺杂的方法实现对Au NCs发光波长和发光强度的调控。如图1(b)所示，将Cd离子掺入到Au_{25}团簇中能够得到$Au_{24}Cd_1$纳米团簇。该方法调控了金簇中的单原子活性位点，增强了金纳米团簇的催化性能[16]。如图1(c)所示，目前，铜、镉、银、铂、锌等离子已被成功地掺入Au NCs[13]，实现了对其发光波长、发光强度、化

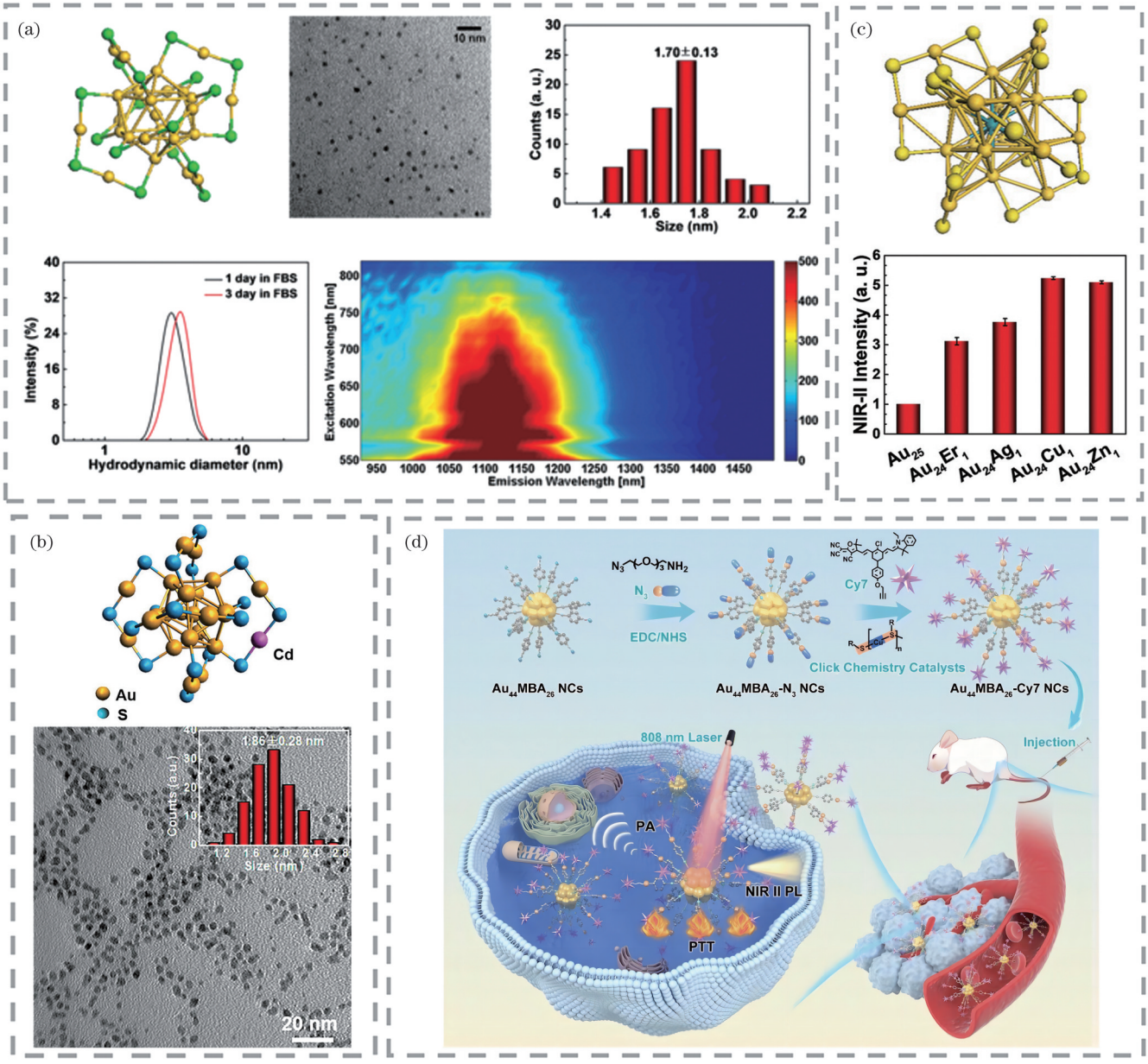

图1 NIR-Ⅱ Au NCs的合成。(a)Au_{25}团簇的结构与表征示意图[13]；(b)$Au_{24}Cd_1$团簇的结构示意图及透射电镜（TEM）图像[16]；(c)通过掺杂金属增强Au_{25}团簇的NIR-Ⅱ荧光[13]；(d)$Au_{44}MBA_{26}$纳米团簇在NIR-Ⅱ荧光和光声成像引导下的癌症光热治疗示意图[15]

Fig. 1 Synthesis of NIR-Ⅱ Au NCs. (a) Schematics of structure and characterization of Au_{25} clusters[13]; (b) schematics of structure and transmission electron microscope (TEM) image of $Au_{24}Cd_1$ clusters[16]; (c) enhancement of NIR-Ⅱ fluorescence of Au_{25} clusters by doping with metals[13]; (d) photothermal treatment of cancer with $Au_{44}MBA_{26}$ nanoclusters guided by NIR-Ⅱ fluorescence and photoacoustic imaging[15]

学活性的调控。但是，这些有毒重金属离子的引入也增加了 Au NCs的毒性，不利于NIR-Ⅱ Au NCs的临床转化。

目前，NIR-Ⅱ Au NCs的发射峰通常位于1000～1100 nm区间，鲜有荧光发射峰超过1100 nm的Au NCs的相关报道，原理上可以通过抑制非辐射衰变的刚性结构设计、高振子强度的强带边跃迁以及诱导快速的辐射衰减等方法来调控NIR-Ⅱ Au NCs的发光波长。例如，Li等[17]报道了NIR-Ⅱ Au NCs中荧光发射的潜在电子跃迁，包括以往被忽略的基态几何结构中振荡强度接近零的最高被占轨道-最低空轨道（HOMO-LUMO）跃迁，并提供了新的原子水平结构剪裁方法。

3 NIR-Ⅱ Au NCs的表面修饰

NIR-Ⅱ Au NCs的表面修饰分子不仅能够提高其水溶性和稳定性，还能赋予NIR-Ⅱ Au NCs的分子靶向性。NIR-Ⅱ Au NCs的荧光发射波长可通过调控金原子数量和表面基团来实现调控[13,18]。目前NIR-Ⅱ Au NCs的表面修饰分子主要有还原性谷胱甘肽[19]、巯基小分子化合物（例如单硫醇、二硫醇和聚乙二醇硫醇配体等）[18]、牛血清白蛋白[20]、环糊精（CD）[21]和小分子蛋白（例如Min-23）[22]等。调控这些分子与金离子的比例不仅能够控制NIR-Ⅱ Au NCs的荧光发射波长，而且还能赋予其分子靶向功能，实现特定功能分子的高灵敏、高分辨NIR-Ⅱ荧光成像。如图2（a）所示，杨

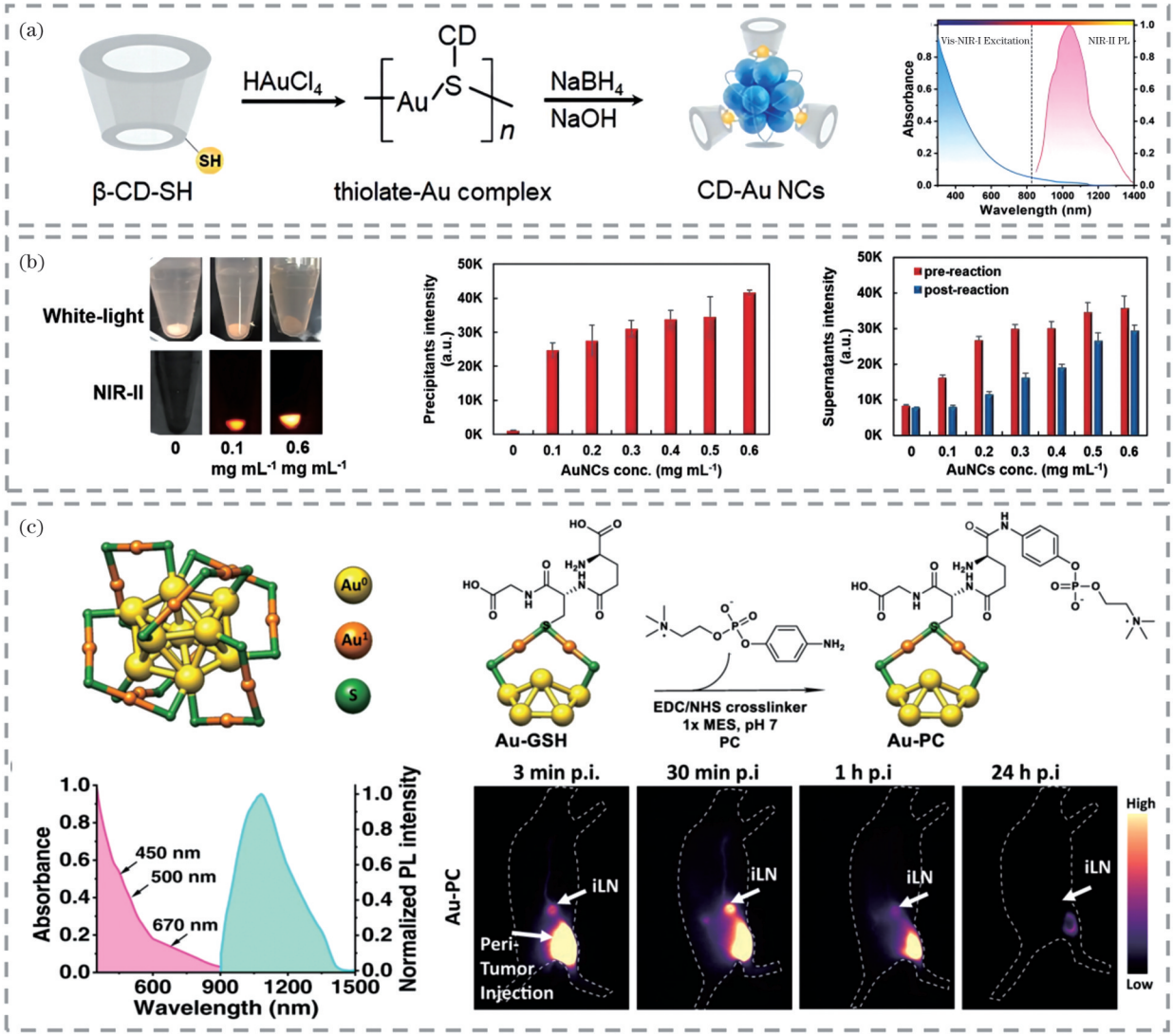

图2 NIR-Ⅱ Au NCs的表面修饰。（a）CD-Au NC的合成过程和紫外荧光光谱[21]；（b）Au NCs和羟基磷灰石（HA）在体外高效结合，显示出明显的NIR-Ⅱ荧光[19]；（c）Au-PC的结构示意图、Au-PC团簇瘤周给药和引流腹股沟淋巴结（iLN）在3 min内显示出高亮度NIR-Ⅱ荧光[23]

Fig. 2 Surface modification of NIR-Ⅱ Au NCs. (a) Synthesis process and ultraviolet fluorescent spectrum of CD-Au NC[21]; (b) Au NCs and hydroxyapatite (HA) bind efficiently *in vitro*, showing obvious NIR-Ⅱ fluorescence[19]; (c) structural diagram of Au-PC, peritumor administration of Au-PC clusters, and draining inguinal lymph node (iLN) showing high brightness NIR-Ⅱ fluorescence within 3 min[23]

黄浩课题组利用硫代环糊精作为金纳米团簇的表面修饰分子，一步还原合成了中心发射波长为1050 nm的NIR-Ⅱ Au NCs，并通过主客体识别技术连接了抗CD326抗体分子，在小鼠模型上实现了乳腺肿瘤的靶向NIR-Ⅱ荧光分子成像[21]。如图2(b)所示，程震团队首次发现还原性谷胱甘肽(GSH)的羧基与骨基质中的羟基磷灰石能发生特异性结合，使得GSH修饰的NIR-Ⅱ Au NCs具有骨靶向的能力[19]。他们利用Au-GSH NCs的这种特性实现了对小鼠骨骼(肋骨和胸椎)的高分辨NIR-Ⅱ荧光成像。另一方面，NIR-Ⅱ Au NCs的尺寸小，血液半衰期短，易非特异性吸附体内的蛋白分子，极大降低了NIR-Ⅱ Au NCs荧光成像的特异性。为了解决这个问题，戴宏杰课题组提出了一种磷酰胆碱(PC)的配体修饰方法，如图2(c)所示，通过NIR-Ⅱ Au NCs表面的羧基与PC的氨基发生的乙酰化反应，将PC修饰到Au-GSH NCs表面(Au-PC)，极大地降低了NIR-Ⅱ Au NCs的非特异性吸附性能[23]。他们利用这种“超级隐形”的Au-PC NCs在4T1和CT26小鼠肿瘤模型上实现了对小鼠前哨淋巴结的高灵敏、高分辨NIR-Ⅱ荧光成像。因此，开发高性能的表面修饰分子，增强NIR-Ⅱ Au NCs的水溶性、稳定性和分子特异性，是提高NIR-Ⅱ Au NCs体内分子靶向性和加速NIR-Ⅱ Au NCs临床转化应用的关键。

4 NIR-Ⅱ Au NCs的生物医学应用

NIR-Ⅱ Au NCs具有良好的生物相容性和优异的荧光性能，在生物医学光子学领域中展现出广阔的应用前景，包括血管的高分辨成像、淋巴管和淋巴结的精确定位、肿瘤的精准诊断和NIR-Ⅱ荧光成像引导治疗等。

4.1 血管成像

血管功能障碍与癌症、脑卒中、心肌梗死等多种危及生命的疾病密切相关。因此，异常血管的可视化对于相关疾病的早期诊断和治疗具有重要意义[24-27]。目前临床上常规的检测异常血管的无创成像方法有计算机断层扫描(CT)、超声和磁共振成像(MRI)，但这些方法都存在空间分辨率低、成像伪影以及成像质量易受操作者影响等问题[28-29]。而超小尺寸(<3 nm)的NIR-Ⅱ Au NCs具有低毒性、可肾脏清除、优异的NIR-Ⅱ荧光性能和深层组织渗透特性，在血管成像领域中受到研究者的广泛关注。如图3(a)所示，Xavier团队利用中心发射波长位于1250 nm的NIR-Ⅱ Au NCs实现对小鼠全身血管网络的高分辨成像，成像深度超过4 mm，空间分辨率提高到59%，实现了骨骼中微小血管的精准可视化[18]。如图3(b)所示，蒋兴宇课题组利用密集的刷状聚乙二醇(PEG)修饰NIR-Ⅱ Au NCs，实现了小鼠血管功能障碍的实时、动态可视化，为溶栓药物的精确使用提供了可视化的指导[30]。如图3(c)所示，张晓东课题组将NIR-Ⅱ $Au_{25}(GSH)_{18}$ NCs用于穿透头皮和颅骨的脑血管的高分辨成像，为脑损伤和脑卒中的基础研究和药物筛选提供了新的成像方法和成像技术[13]。

4.2 淋巴管和淋巴结成像

淋巴管和淋巴结与实体瘤的扩散和转移密切相关。癌细胞通过附着并穿透周围淋巴管进入周围淋巴结，进而逐渐扩散到全身器官和淋巴结上。前哨淋巴结(SLN)是癌症转移的第一站[31]。因此，精准检测出淋巴管和淋巴结里的癌细胞尤其是SLN里的癌细胞对于肿瘤治疗和预后至关重要[32]。淋巴闪烁显像是迄今为止临床肿瘤学中分期评估乳腺癌、黑色素瘤和头颈癌SLN转移的“金标准”[33-34]，但是仍然存在着2%～28%的错误检测率[35]。临床上ICG作为淋巴闪烁显像的对比剂，用于各种实体瘤的淋巴管和淋巴结成像[36-37]，但存在着成像信背比低、非特异性吸附强和代谢快等缺点。最近，戴宏杰课题组开发了PC配体功能化的NIR-Ⅱ Au NCs(Au-PC)，在皮下注射0.5～1.0 h后通过NIR-Ⅱ荧光成像对4T1和CT26肿瘤小鼠模型的前哨淋巴结进行定位，随后被肾脏快速清除[23]。相比于ICG在体内的非特异性结合和成像时间窗不确定的特点，NIR-Ⅱ Au-PC可以对前哨淋巴结进行更清晰、更有针对性的成像，尤其适用于需要快速诊断和干预决策的临床情况。除了这种常见的单配体修饰以外，蒋兴宇团队还开发了双配体/多配体封端的金纳米团簇(GNCs)，如图4(a)所示，显著提高了化疗药物(如甲氨蝶呤)输送到靶淋巴结的效率，实现了药物输运的可视化[38]。虽然NIR-Ⅱ Au NCs在淋巴管和淋巴结荧光成像中的应用取得了初步的成果，但优化NIR-Ⅱ Au NCs的成像剂量和成像时间窗口以及实现特异性检测淋巴结中的癌细胞成像还面临巨大挑战。因此，大动物和非人灵长类动物中的淋巴管和淋巴结成像实验是推动NIR-Ⅱ Au NCs临床转化的基础。

4.3 肿瘤成像

传统的超声、电子计算机断层扫描、磁共振结构成像能够实现疾病演进过程的定性、定量可视化，为疾病的诊断和治疗提供重要指导。分子靶向成像超越了传统的结构成像，可通过分子探针实现特定肿瘤靶点的高灵敏显影，为疾病的早期诊断、疗效监测和预后评估提供了新工具。通过在NIR-Ⅱ Au NCs表面上修饰特异性的靶向分子，设计智能响应的分子功能，能够实现基于NIR-Ⅱ Au NCs的肿瘤靶向荧光成像[39-40]。例如，崔大祥团队通过将抗CD326抗体标记在NIR-Ⅱ Au NCs表面上，实现了MCF-7和MGC-803肿瘤的高灵敏荧光成像和治疗[41]。除了对传统肿瘤的靶向成像以外，NIR-Ⅱ Au NCs还可以实现对胃肠道相关疾病的定位和实时成像。如图4(c)所示，肖艳团队通过将聚

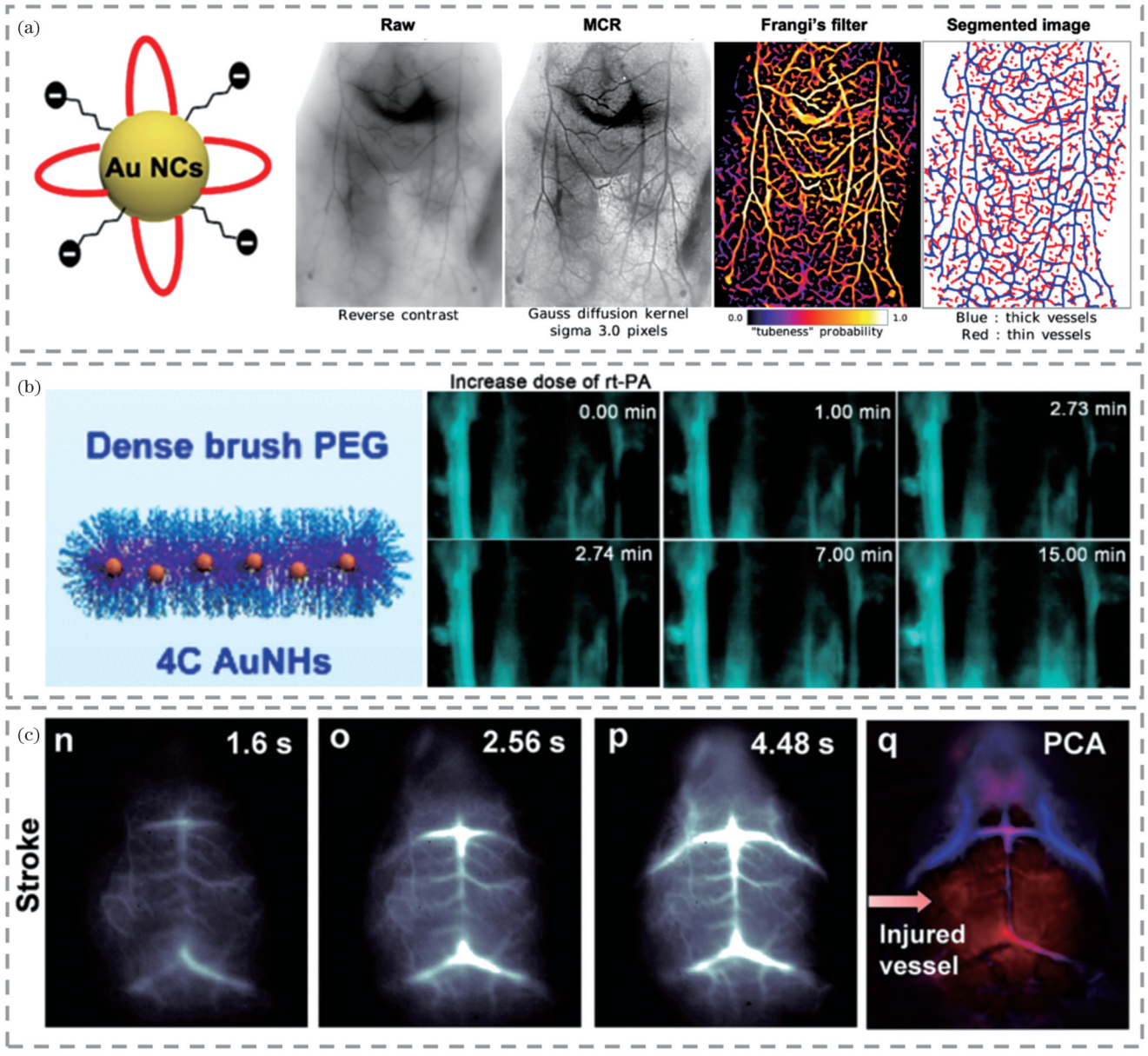

图 3 NIR-Ⅱ Au NCs的血管成像。(a)利用经膜化学反应器(MCR)处理的NIR-Ⅱ Au NCs进行血管的实时荧光成像[18];(b)通过静脉注射NIR-Ⅱ Au NCs,监测高剂量重组组织纤溶酶原激活化剂(rt-PA)给药后的血栓溶解过程[30];(c)利用NIR-Ⅱ Au NCs进行脑卒中小鼠颅骨脑的荧光动态成像[13]

Fig. 3 Vascular imaging of NIR-Ⅱ Au NCs. (a) Real-time vascular fluorescence imaging using NIR-Ⅱ Au NCs treated with membrane chemical reactor (MCR)[18]; (b) thrombolytic process after high-dose recombinant tissue plasminogen activator (rt-PA) is monitored by intravenous administration of NIR-Ⅱ Au NCs[30]; (c) dynamic fluorescence imaging of skull brain of stroke mice using IR-Ⅱ Au NCs[13]

多巴胺(PDA)和亚甲基蓝(MB)与NIR-Ⅱ Au NCs结合(Au NCs@PDA-MB),对摄食、抑酸药物和胃溃疡疾病引起的胃酸变化进行了pH响应性成像,实现了对体内胃酸分泌的监测[42]。此外,李瑞宾课题组首次通过调控金团簇表面的蛋白冠构建了靶向胃肠道的RNase-A包封的Au NCs(RNase-A@Au NCs),如图4(b)所示,能够在胃肠蠕动期间实现胃肠道详细结构的可视化,用于辅助胃肠道相关疾病的诊断[43]。

4.4 成像引导治疗

成像引导治疗是一种先进的可视化治疗技术,能够避免不必要的身体创伤,降低有创治疗的成本,实现病灶精准定位、术中实时反馈、治疗方案优化以及疗效评估。因此,成像引导治疗对于外科手术的术前诊断、术中引导治疗乃至术后体检随访都尤为重要。目前临床上常见的可用于引导治疗的成像方式包括超声、CT、磁共振以及荧光成像等。利用NIR-Ⅱ Au NCs作为示踪剂和药物载体系统,能够实现药物在体内的可视化输运和引导治疗,提高疗效。例如,铂(Pt)是癌症治疗中使用最广泛的化疗药物之一[44-46],GSH可以迅速与之结合形成GSH-Pt偶联物并从癌细胞中输出,

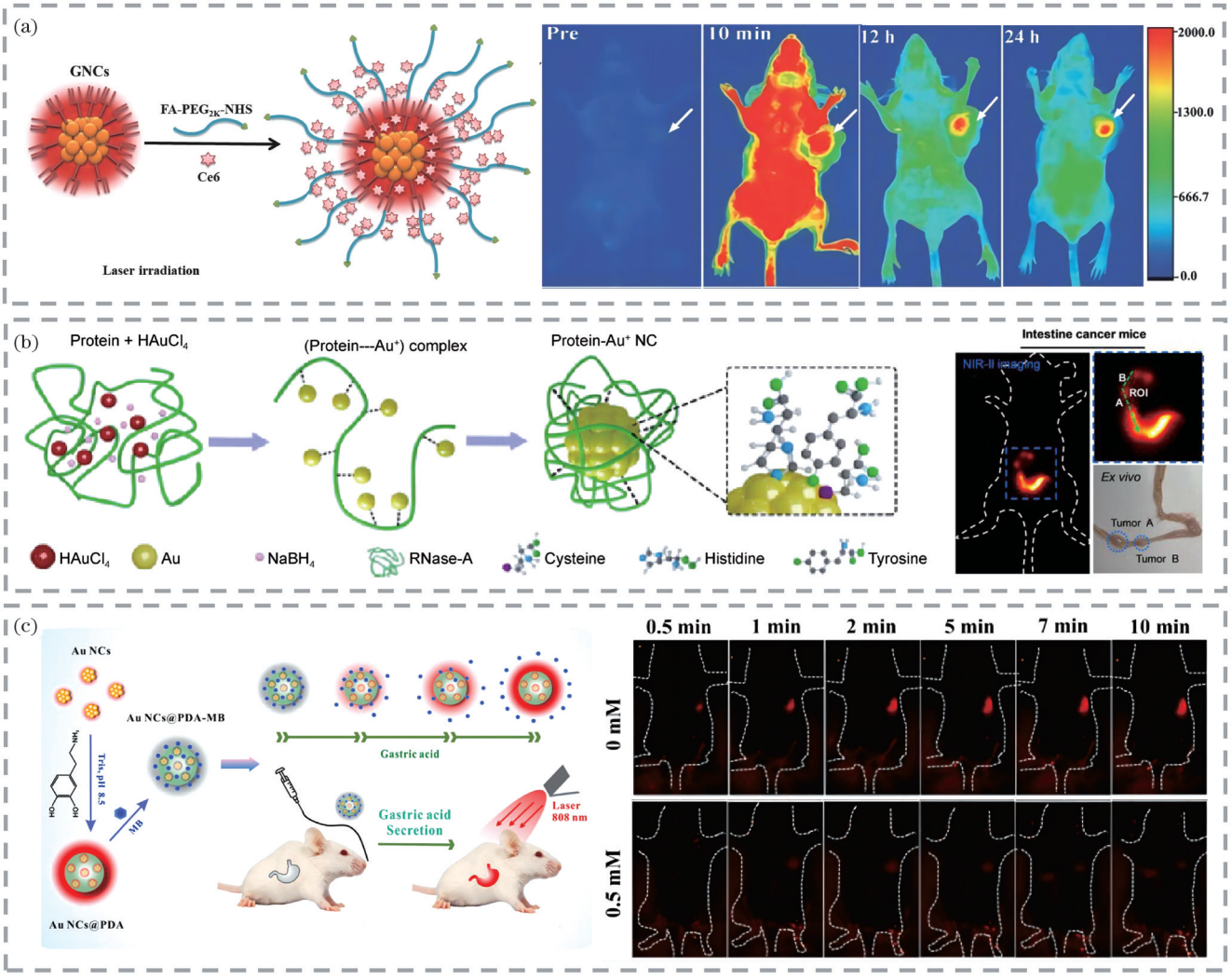

图 4 NIR-Ⅱ Au NCs用于肿瘤靶向荧光成像。(a)静脉注射负载光敏剂 Ce6 的 PEG 功能化金纳米团簇(Ce6@GNCs-PEG)后在肿瘤部位观察到显著的荧光[41];(b)患有肠癌的小鼠通过口服给药 RNase-A@Au NCs 后可观察到肿瘤结节[43];(c)Au NCs@PDA-MB 纳米探针在小鼠体内的胃酸抑制成像[42]

Fig. 4 NIR-Ⅱ Au NCs for tumor targeted fluorescence imaging. (a) Significant fluorescence observed at tumor site after intravenous injection of PEG functionalized gold nanoclusters loaded with photosensitizer Ce6 (Ce6@GNCs-PEG)[41]; (b) tumor nodules can be observed in mice with bowel cancer after oral administration of RNase-A@Au NCs[43]; (c) Au NCs@PDA-MB nanoprobes for *in vivo* gastric acid inhibition imaging of mice[42]

从而使 Pt 药物失活[47-49]。因此,肿瘤细胞中 GSH 的过表达被普遍认为是导致铂耐药的重要因素[50]。喻志强团队利用 NIR-Ⅱ Au NCs 装载化疗药物铂(Au NCs-Pt),在增强铂依赖的化疗效果的同时,通过高分辨率 NIR-Ⅱ 成像,实现深部组织中铂转运过程的可视化,提高治疗效率[51]。

不仅如此,NIR-Ⅱ Au NCs 具有良好的表面可修饰性,能够联合其他成像分子、光敏剂或免疫靶点等[12,52-54],实现 NIR-Ⅱ 荧光成像乃至多模态成像引导下的包含癌症光动力治疗(PDT)[17]、光热治疗(PTT)[55]、免疫治疗[56]、化学动力疗法[57-62]等在内的一系列联合治疗,并显著提高了癌症诊断的准确性和疗效[63-65]。杨戈课题组通过将 $Au_{44}MBA_{26}$ 与光敏剂 Cy7 结合,设计出一种新型 NIR-Ⅱ Au NCs 治疗探针,能够在 NIR-Ⅱ 荧光和光声(PA)成像引导下实现高灵敏度和特异性的癌症治疗[15]。如图 5(a)所示,黄鹏团队采用二氧化锰包裹涂有二氧化硅涂层的 NIR-Ⅱ 金纳米棒(GNR@SiO_2@MnO_2),用于肿瘤微环境响应性 PA/MRI 双模态成像引导下的 NIR-Ⅱ 光热-化学动力学治疗,并取得了显著的联合疗效[66]。此外,利用 NIR-Ⅱ Au NCs 与免疫检查点抑制剂的偶联[56],在 NIR-Ⅱ 荧光成像引导下可以进行深部肿瘤的治疗,同时利用其光热性质,可实现 PTT、PDT[67]及癌症免疫治疗等多重联合治疗。

4.5 其他应用

除了肿瘤外,氧化应激和炎症等在临床中也十分常见[68]。然而,目前的分子制剂不能在实时监测炎症的同时减轻炎症。最近,NIR-Ⅱ Au NCs 在氧化应激

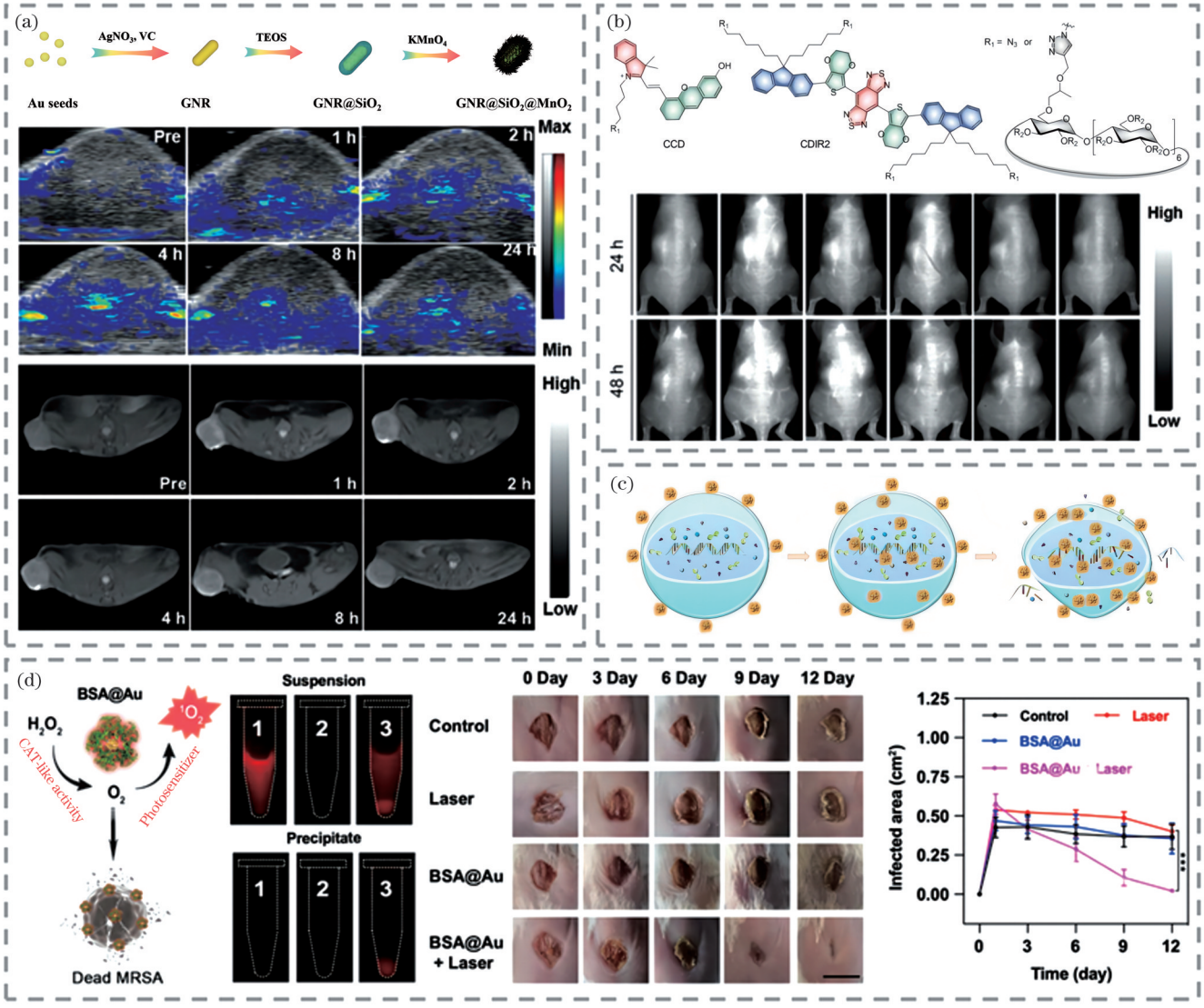

图 5 NIR-Ⅱ Au NCs用于炎症和抗菌治疗。(a)用于体内PA和MRI评估的NIR-Ⅱ Au NCs纳米诊断剂[66];(b)用于监测急性肾损伤的NIR-Ⅱ Au NCs探针的化学结构示意图及静脉注射后不同时间点肾脏的NIR-Ⅱ荧光强度[74];(c)Au NCs的抗菌机理示意图[78];(d)牛血清白蛋白包裹的Au NCs(BSA@Au)具有过氧化氢酶(CAT)样活性和$^1O_2$生成能力,联合激光治疗细菌感染,伤口快速愈合[20]

Fig. 5 NIR-Ⅱ Au NCs used for inflammatory and antimicrobial therapy. (a) NIR-Ⅱ Au NCs nano diagnostic agent for *in vivo* PA and MRI assessment[66]; (b) schematic chemical structure of NIR-Ⅱ Au NCs probe for monitoring acute kidney injury and NIR-Ⅱ fluorescence intensity of kidney at different time points after intravenous injection[74]; (c) schematic of antibacterial mechanism of Au NCs[78]; (d) bovine serum albumin-encapsulated Au NCs (BSA@Au) possessing catalase (CAT)-like activity and $^1O_2$ producing capacity, which can be combined with laser therapy for bacterial infection to realized rapid wound healing[20]

和炎症相关疾病治疗中的应用取得了重要进展,该项研究也受到了广泛关注。NIR-Ⅱ Au NCs不仅能够通过荧光成像定位病灶,还可以通过自身的活性和搭载的药物分子消除氧化应激和减轻炎症反应[69-70]。例如,负载NIR-Ⅱ Au NCs的聚甲基丙烯酸乙酯纳米粒子(Au-PEMA NPs)在体外显示出了摄取巨噬细胞的性能,该性能依赖时间和剂量,并诱导了脂多糖(LPS)激活的巨噬细胞抗炎反应和一氧化氮水平的强烈下调[71]。在氧化应激相关疾病中,急性肾损伤(AKI)尤为常见,其作为临床上高发病率和高死亡率的肾脏疾病之一,早期诊断和干预可以有效避免严重并发症的发生[72-74]。如图5(b)所示,Pu团队开发了一种具有高肾脏清除率的NIR-Ⅱ Au NCs探针,用于小鼠的实时无创急性肾损伤监测[75]。此外,张晓东团队通过原子工程在Au_{22}团簇上创建了铜单原子活性位点($Au_{21}Cu_1$)[76]及在Au_{25}团簇上创建了Cd单原子活性位点($Au_{24}Cd_1$)[16],减轻了氧化应激和炎症对肾和大脑的损伤,同时具有对氧化应激和炎症相关疾病(如AKI)进行实时成像和早期干预的巨大潜力。

细菌感染也是目前疾病治疗的重心之一。细菌感染与癌症发病率密切相关,据估计,细菌感染因素个数约占所有人类肿瘤发病因素个数的20%[77]。

NIR-Ⅱ Au NCs本身具有杀菌能力，因此在抗菌治疗方面有着广阔的应用前景。如图5(c)所示，谢建平课题组采用可追踪的NIR-Ⅱ Au NCs观察抗菌过程，发现了NIR-Ⅱ Au NCs的抗菌机理：NIR-Ⅱ Au NCs首先附着在细菌膜上，穿透细菌膜后在细菌内部积聚，然后诱导活性氧(ROS)破坏细菌膜并最终杀死细菌[78]。NIR-Ⅱ Au NCs具有NIR-Ⅱ发光的特性，使得抗菌治疗可视化，除此之外，如图5(d)所示，NIR-Ⅱ Au NCs还具有极好的过氧化氢酶样活性，能够催化分解多余的H_2O_2，在肿瘤和细菌感染组织的微环境中产生O_2，从而增强PDT的抗菌效果[20]。

5 总结与展望

NIR-Ⅱ Au NCs是生物医学光子学研究的强大候选者，它表现出合成便捷、成分单一、发光波长可调谐、生物相容性好、体内可清除、易于靶向修饰等独特优势，已经在肿瘤诊断、药物输运、多模态成像等领域中展示出广阔的应用前景[79-85]。但是，NIR-Ⅱ Au NCs的进一步应用和临床转化还面临着诸多的挑战：1) 现有的NIR-Ⅱ Au NCs合成方法还存在产率低和无法实现大规模制备的问题，急需发展更加高效的制备方法和工艺；2) 现有的NIR-Ⅱ Au NCs的中心发光波长小于1300 nm，荧光量子产率小于10%，迫切需要改进合成方法以增大其发光波长和提高其NIR-Ⅱ荧光量子产率；3) 需要进一步研究NIR-Ⅱ Au NCs的临床使用场景，阐明其确切的临床价值，更好地用于疾病诊疗。未来可以进一步拓展NIR-Ⅱ Au NCs的应用范围，包括心血管疾病、炎症成像、术中肿瘤边界可视化等，以更好地满足临床转化需求，为维护人们的健康发挥重要的作用。

参 考 文 献

[1] 刘嘉慧，杨燕青，马睿，等. 有机近红外二区荧光探针研究进展[J]. 中国激光，2023，50(21)：2107101.
Liu J H，Yang Y Q，Ma R，et al. Research progress of organic NIR-Ⅱ fluorescent probes[J]. Chinese Journal of Lasers，2023，50(21)：2107101.

[2] 冯哲，钱骏. 近红外二区荧光活体生物成像技术研究进展[J]. 激光与光电子学进展，2022，59(6)：0617001.
Feng Z，Qian J. Advances on *in vivo* fluorescence bioimaging in the second near-infrared window[J]. Laser & Optoelectronics Progress，2022，59(6)：0617001.

[3] 韦族武，杨森，吴名，等. 近红外二区荧光手术导航探针研究进展[J]. 中国激光，2022，49(5)：0507102.
Wei Z W，Yang S，Wu M，et al. Recent progress in near-infrared-Ⅱ fluorescence imaging probes for fluorescence surgical navigation[J]. Chinese Journal of Lasers，2022，49(5)：0507102.

[4] Welsher K，Liu Z，Sherlock S P，et al. A route to brightly fluorescent carbon nanotubes for near-infrared imaging in mice[J]. Nature Nanotechnology，2009，4(11)：773-780.

[5] Bruns O T，Bischof T S，Harris D K，et al. Next-generation *in vivo* optical imaging with short-wave infrared quantum dots[J]. Nature Biomedical Engineering，2017，1：56.

[6] Ma Z R，Wang F F，Zhong Y T，et al. Cross-link-functionalized nanoparticles for rapid excretion in nanotheranostic applications[J]. Angewandte Chemie (International Ed. in English)，2020，59(46)：20552-20560.

[7] Zhong Y T，Ma Z R，Wang F F，et al. *In vivo* molecular imaging for immunotherapy using ultra-bright near-infrared-Ⅱ b rare-earth nanoparticles[J]. Nature Biotechnology，2019，37(11)：1322-1331.

[8] Fan Y，Wang P Y，Lu Y Q，et al. Lifetime-engineered NIR-Ⅱ nanoparticles unlock multiplexed *in vivo* imaging[J]. Nature Nanotechnology，2018，13(10)：941-946.

[9] Liu S J，Ou H L，Li Y Y，et al. Planar and twisted molecular structure leads to the high brightness of semiconducting polymer nanoparticles for NIR-Ⅱ a fluorescence imaging[J]. Journal of the American Chemical Society，2020，142(35)：15146-15156.

[10] Xu R T，Jiao D，Long Q，et al. Highly bright aggregation-induced emission nanodots for precise photoacoustic/NIR-Ⅱ fluorescence imaging-guided resection of neuroendocrine neoplasms and sentinel lymph nodes[J]. Biomaterials，2022，289：121780.

[11] Antaris A L，Chen H，Cheng K，et al. A small-molecule dye for NIR-Ⅱ imaging[J]. Nature Materials，2016，15(2)：235-242.

[12] Han T Y，Wang Y J，Ma S J，et al. Near-infrared carbonized polymer dots for NIR-Ⅱ bioimaging[J]. Advanced Science，2022，9(30)：e2203474.

[13] Liu H L，Hong G S，Luo Z T，et al. Atomic-precision gold clusters for NIR-Ⅱ imaging[J]. Advanced Materials，2019，31(46)：e1901015.

[14] Hu Z H，Fang C，Li B，et al. First-in-human liver-tumour surgery guided by multispectral fluorescence imaging in the visible and near-infrared-I/Ⅱ windows[J]. Nature Biomedical Engineering，2020，4(3)：259-271.

[15] Yang G，Mu X，Pan X X，et al. Ligand engineering of Au_{44} nanoclusters for NIR-Ⅱ luminescent and photoacoustic imaging-guided cancer photothermal therapy[J]. Chemical Science，2023，14(16)：4308-4318.

[16] Huang Y，Chen K，Liu L，et al. Single atom-engineered NIR-Ⅱ gold clusters with ultrahigh brightness and stability for acute kidney injury[J]. Small，2023，19(30)：e2300145.

[17] Li Q，Zeman C J，Ma Z R，et al. Bright NIR-Ⅱ photoluminescence in rod-shaped icosahedral gold nanoclusters[J]. Small，2021，17(11)：e2007992.

[18] Yu Z X，Musnier B，Wegner K D，et al. High-resolution shortwave infrared imaging of vascular disorders using gold nanoclusters[J]. ACS Nano，2020，14(4)：4973-4981.

[19] Li D L，Liu Q，Qi Q R，et al. Gold nanoclusters for NIR-Ⅱ fluorescence imaging of bones[J]. Small，2020，16(43)：e2003851.

[20] Dan Q，Yuan Z，Zheng S，et al. Gold nanoclusters-based NIR-Ⅱ photosensitizers with catalase-like activity for boosted photodynamic therapy[J]. Pharmaceutics，2022，14(8)：1645.

[21] Song X R，Zhu W，Ge X G，et al. A new class of NIR-Ⅱ gold nanocluster-based protein biolabels for *in vivo* tumor-targeted imaging[J]. Angewandte Chemie (International Ed. in English)，2021，60(3)：1306-1312.

[22] Kong Y F，Santos-Carballal D，Martin D，et al. A NIR-Ⅱ-emitting gold nanocluster-based drug delivery system for smartphone-triggered photodynamic theranostics with rapid body clearance[J]. Materials Today，2021，51：96-107.

[23] Baghdasaryan A，Wang F F，Ren F Q，et al. Phosphorylcholine-conjugated gold-molecular clusters improve signal for Lymph Node NIR-Ⅱ fluorescence imaging in preclinical cancer models[J]. Nature Communications，2022，13：5613.

[24] Krishnamurthi R V，Feigin V L，Forouzanfar M H，et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010：findings from the Global Burden of Disease Study 2010[J]. The Lancet. Global Health，2013，1(5)：e259-e281.

[25] Pasterkamp G，den Ruijter H M，Libby P. Temporal shifts in clinical presentation and underlying mechanisms of atherosclerotic disease[J]. Nature Reviews Cardiology，2017，14(1)：21-29.

[26] Cheng S Y，Hang C，Ding L，et al. Electronic blood vessel[J]. Matter，2020，3(5)：1664-1684.

[27] Hong G S, Diao S, Chang J L, et al. Through-skull fluorescence imaging of the brain in a new near-infrared window[J]. Nature Photonics, 2014, 8(9): 723-730.
[28] Goldfarb J W, Weber J. Trends in cardiovascular MRI and CT in the U.S. medicare population from 2012 to 2017[J]. Radiology: Cardiothoracic Imaging, 2021, 3(1): e200112.
[29] Nishimiya K, Matsumoto Y, Shimokawa H. Recent advances in vascular imaging[J]. Arteriosclerosis, Thrombosis, and Vascular Biology, 2020, 40(12): e313-e321.
[30] Zhou T Y, Zha M L, Tang H, et al. Controlling NIR-Ⅱ emitting gold organic/inorganic nanohybrids with tunable morphology and surface PEG density for dynamic visualization of vascular dysfunction[J]. Chemical Science, 2023, 14(33): 8842-8849.
[31] Morton D L, Wen D R, Wong J H, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma[J]. Archives of Surgery, 1992, 127(4): 392-399.
[32] Faries M B, Testori A A E, Gershenwald J E. Sentinel node biopsy for primary cutaneous melanoma[J]. Annals of Oncology, 2021, 32(3): 290-292.
[33] Dogan N U, Dogan S, Favero G, et al. The basics of sentinel lymph node biopsy: anatomical and pathophysiological considerations and clinical aspects[J]. Journal of Oncology, 2019, 2019: 3415630.
[34] Moncayo V M, Aarsvold J N, Alazraki N P. Lymphoscintigraphy and sentinel nodes[J]. Journal of Nuclear Medicine, 2015, 56(6): 901-907.
[35] Chahid Y, Qiu X B, van de Garde E M W, et al. Risk factors for nonvisualization of the sentinel lymph node on lymphoscintigraphy in breast cancer patients[J]. EJNMMI Research, 2021, 11(1): 54.
[36] Ballardini B, Santoro L, Sangalli C, et al. The indocyanine green method is equivalent to the ^{99m}Tc-labeled radiotracer method for identifying the sentinel node in breast cancer: a concordance and validation study[J]. European Journal of Surgical Oncology (EJSO), 2013, 39(12): 1332-1336.
[37] Kim J H, Ku M, Yang J, et al. Recent developments of ICG-guided sentinel lymph node mapping in oral cancer[J]. Diagnostics, 2021, 11(5): 891.
[38] Pang Z Y, Yan W X, Yang J E, et al. Multifunctional gold nanoclusters for effective targeting, near-infrared fluorescence imaging, diagnosis, and treatment of cancer lymphatic metastasis [J]. ACS Nano, 2022, 16(10): 16019-16037.
[39] Zhou C, Long M, Qin Y P, et al. Luminescent gold nanoparticles with efficient renal clearance[J]. Angewandte Chemie (International Ed. in English), 2011, 50(14): 3168-3172.
[40] Liu J B, Yu M X, Zhou C, et al. Passive tumor targeting of renal-clearable luminescent gold nanoparticles: long tumor retention and fast normal tissue clearance[J]. Journal of the American Chemical Society, 2013, 135(13): 4978-4981.
[41] Zhang C L, Li C, Liu Y L, et al. Gold nanoclusters-based nanoprobes for simultaneous fluorescence imaging and targeted photodynamic therapy with superior penetration and retention behavior in tumors[J]. Advanced Functional Materials, 2015, 25 (8): 1314-1325.
[42] Liang M, Hu Q, Yi S X, et al. Development of an Au nanoclusters based activatable nanoprobe for NIR-Ⅱ fluorescence imaging of gastric acid[J]. Biosensors and Bioelectronics, 2023, 224: 115062.
[43] Wang W L, Kong Y F, Jiang J, et al. Engineering the protein corona structure on gold nanoclusters enables red-shifted emissions in the second near-infrared window for gastrointestinal imaging[J]. Angewandte Chemie (International Ed. in English), 2020, 59(50): 22431-22435.
[44] Johnstone T C, Suntharalingam K, Lippard S J. The next generation of platinum drugs: targeted Pt(Ⅱ) agents, nanoparticle delivery, and Pt(Ⅳ) prodrugs[J]. Chemical Reviews, 2016, 116 (5): 3436-3486.
[45] He S S, Li C, Zhang Q F, et al. Tailoring platinum(Ⅳ) amphiphiles for self-targeting all-in-one assemblies as precise multimodal theranostic nanomedicine[J]. ACS Nano, 2018, 12(7): 7272-7281.
[46] Cong Y W, Xiao H H, Xiong H J, et al. Dual drug backboned shattering polymeric theranostic nanomedicine for synergistic eradication of patient-derived lung cancer[J]. Advanced Materials, 2018, 30(11): 1706220.
[47] Kurokawa H, Ishida T, Nishio K, et al. γ-glutamylcysteine synthetase gene overexpression results in increased activity of the ATP-dependent glutathione S-conjugate export pump and cisplatin resistance[J]. Biochemical and Biophysical Research Communications, 1995, 216(1): 258-264.
[48] Kelland L. The resurgence of platinum-based cancer chemotherapy [J]. Nature Reviews Cancer, 2007, 7(8): 573-584.
[49] Goto S, Iida T, Cho S, et al. Overexpression of glutathione S-transferase π enhances the adduct formation of cisplatin with glutathione in human cancer cells[J]. Free Radical Research, 1999, 31(6): 549-558.
[50] Ling X, Chen X, Riddell I A, et al. Glutathione-scavenging poly (disulfide amide) nanoparticles for the effective delivery of Pt(Ⅳ) prodrugs and reversal of cisplatin resistance[J]. Nano Letters, 2018, 18(7): 4618-4625.
[51] Yang Y Y, Yu Y J, Chen H, et al. Illuminating platinum transportation while maximizing therapeutic efficacy by gold nanoclusters *via* simultaneous near-infrared-I/Ⅱ imaging and glutathione scavenging[J]. ACS Nano, 2020, 14(10): 13536-13547.
[52] Wang Y, Qi K, Yu S S, et al. Revealing the intrinsic peroxidase-like catalytic mechanism of heterogeneous single-atom Co-MoS_2 [J]. Nano-Micro Letters, 2019, 11(1): 102.
[53] Yan R Q, Hu Y X, Liu F, et al. Activatable NIR fluorescence/MRI bimodal probes for *in vivo* imaging by enzyme-mediated fluorogenic reaction and self-assembly[J]. Journal of the American Chemical Society, 2019, 141(26): 10331-10341.
[54] Sun W J, Luo L, Feng Y S, et al. Aggregation-induced emission gold clustoluminogens for enhanced low-dose X-ray-induced photodynamic therapy[J]. Angewandte Chemie (International Ed. in English), 2020, 59(25): 9914-9921.
[55] Li Z F, Wang S L, Zhao J J, et al. Gold nanocluster encapsulated nanorod for tumor microenvironment simultaneously activated NIR-Ⅱ photoacoustic/photothermal imaging and cancer therapy [J]. Advanced Therapeutics, 2023, 6(4): 2200350.
[56] Yang G, Pan X X, Feng W B, et al. Engineering Au_{44} nanoclusters for NIR-Ⅱ luminescence imaging-guided photoactivatable cancer immunotherapy[J]. ACS Nano, 2023, 17 (16): 15605-15614.
[57] Fan W P, Bu W B, Shen B, et al. Intelligent MnO_2 nanosheets anchored with upconversion nanoprobes for concurrent pH-/H_2O_2-responsive UCL imaging and oxygen-elevated synergetic therapy [J]. Advanced Materials, 2015, 27(28): 4155-4161.
[58] Gordijo C R, Abbasi A Z, Ali Amini M, et al. Design of hybrid MnO_2-polymer-lipid nanoparticles with tunable oxygen generation rates and tumor accumulation for cancer treatment[J]. Advanced Functional Materials, 2015, 25(12): 1858-1872.
[59] Wang Z Z, Zhang Y, Ju E G, et al. Biomimetic nanoflowers by self-assembly of nanozymes to induce intracellular oxidative damage against hypoxic tumors[J]. Nature Communications, 2018, 9: 3334.
[60] Lin L S, Song J B, Song L, et al. Simultaneous fenton-like ion delivery and glutathione depletion by MnO_2-based nanoagent to enhance chemodynamic therapy[J]. Angewandte Chemie International Edition, 2018, 57(18): 4902-4906.
[61] He T, Qin X L, Jiang C, et al. Tumor pH-responsive metastable-phase manganese sulfide nanotheranostics for traceable hydrogen sulfide gas therapy primed chemodynamic therapy[J]. Theranostics, 2020, 10(6): 2453-2462.
[62] Zhao H, Wang H, Li H R, et al. Magnetic and near-infrared-Ⅱ fluorescence Au-Gd nanoclusters for imaging-guided sensitization

of tumor radiotherapy[J]. Nanoscale Advances, 2022, 4(7): 1815-1826.
[63] Ding B B, Zheng P, Ma P A, et al. Manganese oxide nanomaterials: synthesis, properties, and theranostic applications [J]. Advanced Materials, 2020, 32(10): 1905823.
[64] Chen Q, Feng L Z, Liu J J, et al. Intelligent albumin-MnO_2 nanoparticles as pH-/H_2O_2-responsive dissociable nanocarriers to modulate tumor hypoxia for effective combination therapy[J]. Advanced Materials, 2016, 28(33): 7129-7136.
[65] Fu L H, Hu Y R, Qi C, et al. Biodegradable manganese-doped calcium phosphate nanotheranostics for traceable cascade reaction-enhanced anti-tumor therapy[J]. ACS Nano, 2019, 13(12): 13985-13994.
[66] He T, Jiang C, He J, et al. Manganese-dioxide-coating-instructed plasmonic modulation of gold nanorods for activatable duplex-imaging-guided NIR-Ⅱ photothermal-chemodynamic therapy[J]. Advanced Materials, 2021, 33(13): 2008540.
[67] Lillo C R, Calienni M N, Rivas Aiello B, et al. BSA-capped gold nanoclusters as potential theragnostic for skin diseases: photoactivation, skin penetration, *in vitro*, and *in vivo* toxicity[J]. Materials Science and Engineering: C, 2020, 112: 110891.
[68] Sun S, Liu H L, Xin Q, et al. Atomic engineering of clusterzyme for relieving acute neuroinflammation through lattice expansion[J]. Nano Letters, 2021, 21(6): 2562-2571.
[69] Zhou R B, Ohulchanskyy T Y, Xu Y J, et al. Tumor-microenvironment-activated NIR-Ⅱ nanotheranostic platform for precise diagnosis and treatment of colon cancer[J]. ACS Applied Materials & Interfaces, 2022, 14(20): 23206-23218.
[70] Jana D, He B, Chen Y, et al. A defect-engineered nanozyme for targeted NIR-Ⅱ photothermal immunotherapy of cancer[J]. Advanced Materials, 2022: 2206401.
[71] Moskalevska I, Faure V, Haye L, et al. Intracellular accumulation and immunological response of NIR-Ⅱ polymeric nanoparticles[J]. International Journal of Pharmaceutics, 2023, 630: 122439.
[72] Huang J G, Lü Y, Li J C, et al. A renal-clearable duplex optical reporter for real-time imaging of contrast-induced acute kidney injury[J]. Angewandte Chemie (International Ed. in English), 2019, 58(49): 17796-17804.
[73] Zhang X, Chen Y, He H S, et al. ROS/RNS and base dual activatable merocyanine-based NIR-Ⅱ fluorescent molecular probe for *in vivo* biosensing[J]. Angewandte Chemie International Edition, 2021, 60(50): 26337-26341.
[74] Yu M X, Zhou J C, Du B J, et al. Noninvasive staging of kidney dysfunction enabled by renal-clearable luminescent gold nanoparticles[J]. Angewandte Chemie International Edition, 2016, 55(8): 2787-2791.
[75] Huang J G, Xie C, Zhang X D, et al. Renal-clearable molecular semiconductor for second near-infrared fluorescence imaging of kidney dysfunction[J]. Angewandte Chemie (International Ed. in English), 2019, 58(42): 15120-15127.
[76] Ma H Z, Zhang X N, Liu L, et al. Bioactive NIR-Ⅱ gold clusters for three-dimensional imaging and acute inflammation inhibition[J]. Science Advances, 2023, 9(31): eadh7828.
[77] van Elsland D, Neefjes J. Bacterial infections and cancer[J]. EMBO Reports, 2018, 19(11): e46632.
[78] Zheng K Y, Setyawati M I, Leong D T, et al. Observing antimicrobial process with traceable gold nanoclusters[J]. Nano Research, 2021, 14(4): 1026-1033.
[79] Katla S K, Zhang J, Castro E, et al. Atomically precise $Au_{25}(SG)_{18}$ nanoclusters: rapid single-step synthesis and application in photothermal therapy[J]. ACS Applied Materials & Interfaces, 2018, 10(1): 75-82.
[80] Zhang X D, Chen J, Luo Z T, et al. Enhanced tumor accumulation of sub-2 nm gold nanoclusters for cancer radiation therapy[J]. Advanced Healthcare Materials, 2014, 3(1): 133-141.
[81] Xu J, Yu M X, Peng C Q, et al. Dose dependencies and biocompatibility of renal clearable gold nanoparticles: from mice to non-human primates[J]. Angewandte Chemie (International Ed. in English), 2018, 57(1): 266-271.
[82] Zhang X D, Luo Z T, Chen J, et al. Storage of gold nanoclusters in muscle leads to their biphasic in vivo clearance[J]. Small, 2015, 11(14): 1683-1690.
[83] Yan R J, Sun S, Yang J, et al. Nanozyme-based bandage with single-atom catalysis for brain trauma[J]. ACS Nano, 2019, 13 (10): 11552-11560.
[84] Mu X Y, Wang J Y, Li Y H, et al. Redox trimetallic nanozyme with neutral environment preference for brain injury[J]. ACS Nano, 2019, 13(2): 1870-1884.
[85] Hao W T, Liu S J, Liu H L, et al. *In vivo* neuroelectrophysiological monitoring of atomically precise Au_{25} clusters at an ultrahigh injected dose[J]. ACS Omega, 2020, 5(38): 24537-24545.

NIR-Ⅱ Fluorescent Gold Nanoclusters for Biomedical Photonics: Advances and Challenges

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Abstract

Significance Recently, fluorescence imaging in the second near-infrared window (NIR-Ⅱ, 1000–1700 nm) has attracted widespread attention from researchers. Compared with visible light window (300–550 nm) and first near-infrared window (NIR-I, 600–950 nm) imaging, NIR-Ⅱ fluorescence imaging exhibits unique advantages such as high tissue penetration (on the order of centimeters), high resolution (on the order of nanometers), and low background. NIR-Ⅱ fluorescent gold nanoclusters (NIR-Ⅱ Au NCs) represent a category of nano-materials with exceptional clinical translational potential. NIR-Ⅱ Au NCs possess singular advantages of monomeric

composition, stable performance, small size (<3 nm), and renal clearance capability. They have been applied in various fields, including tumors, cardiovascular diseases, bacterial infections, neurosciences, and implantable medical devices, demonstrating significant potential applications and promising clinical translation prospects in the realm of high-sensitivity, high-resolution, and deep-tissue molecular imaging of major disease biomarkers.

Progress In this review, we initially introduce the synthesis methods of NIR-Ⅱ Au NCs, discussing the challenges of low yield and scalable production. Subsequently, we delve into the surface modulation techniques for NIR-Ⅱ Au NCs, and methods to regulate the cluster surface structure, composition, and morphology for enhancing their emission wavelengths and fluorescence quantum yields. We then summarize the latest research advancements of NIR-Ⅱ Au NCs in vascular imaging, lymphatic vessel and lymph node imaging, tumor imaging, and imaging-guided therapy. Finally, we discuss the opportunities and challenges faced by NIR-Ⅱ Au NCs in the field of biomedical photonics.

Conclusions and Prospects NIR-Ⅱ Au NCs stand as potent candidates in the realm of biomedical photonics research, showcasing advantages of convenient synthesis, singular composition, tunable emission wavelength, good biocompatibility, *in vivo* clearance, and ease of targeted modification. They have demonstrated promising applications in tumor diagnosis, drug delivery, and multimodal imaging. However, further application and clinical translation of NIR-Ⅱ Au NCs encounter numerous challenges: 1) Existing synthesis methods of NIR-Ⅱ Au NCs suffer from low yield and lack of large-scale macro production processes, necessitating the development of more efficient preparation methods and processes. 2) The central emission wavelengths of existing NIR-Ⅱ Au NCs are less than 1300 nm, with a fluorescence quantum yield below 10%, urgently requiring improved synthesis methods to increase their emission wavelengths and enhance their NIR-Ⅱ fluorescence quantum yields. 3) The clinical use scenarios of NIR-Ⅱ Au NCs require further investigation to elucidate their precise clinical value and better serve disease diagnosis and treatment. Future research can expand into other application areas, including cardiovascular diseases, inflammation imaging, and intraoperative tumor boundary visualization, to better meet clinical translation needs and play a crucial role in safeguarding public health.

Key words bio-optics; gold nanocluster; near-infrared-Ⅱ fluorescence; biomedical photonics; biological imaging; imaging-guided therapy