Literature Report

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Perspective

Advanced Fluorescence Imaging Technology in the Near-Infrared-II Window for Biomedical Applications

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研究领域

Inorganic functional nanomaterials
Biomacromolecular self-assembly
Molecular imaging and their applications in biomedicine

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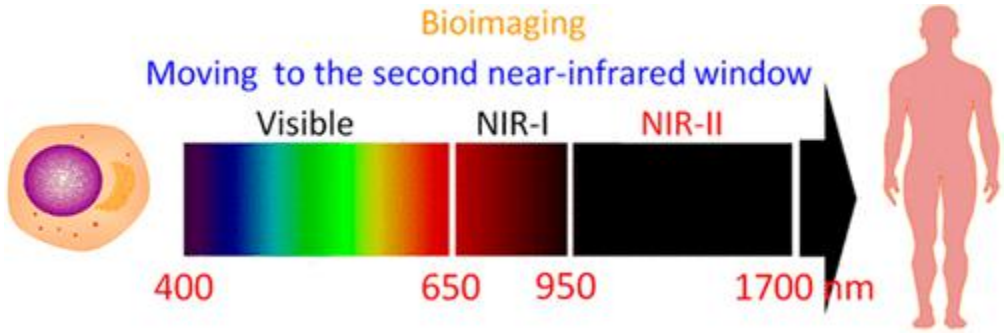
Introduction



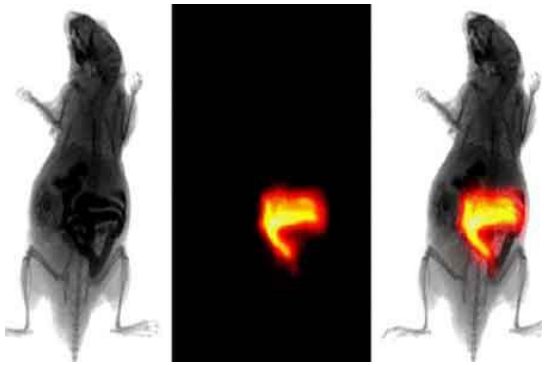
一般人的眼睛可以感知的电磁波的波长在400 ~ 780nm之间。

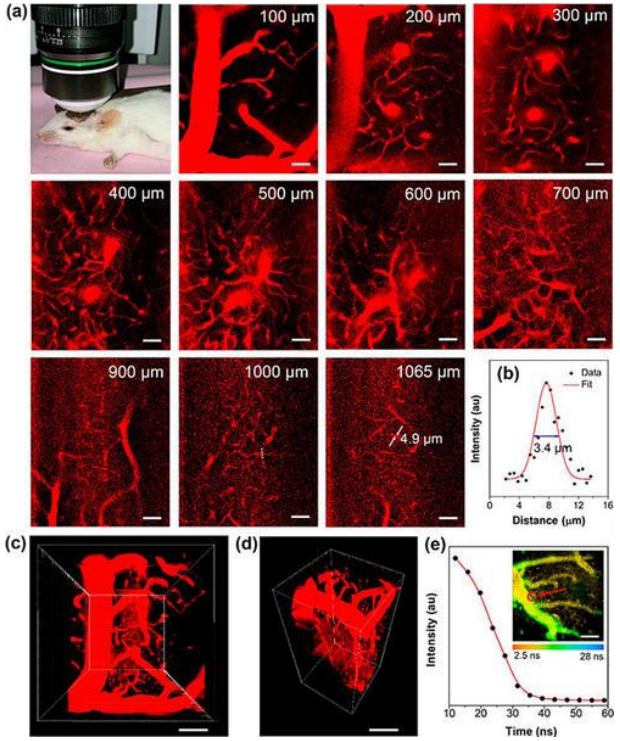
近红外光（Near Infrared，NIR），按ASTM（美国试验和材料检测协会）定义是指波长在780 ~ 2526nm范围内的电磁波，习惯上又将近红外区划分为近红外短波（780~1100nm）和近红外长波（1100~2526nm）两个区域。

相比于可见光，红外光在生物组织中穿透能力更强，穿透深度可达厘米量级，被称为“生物组织的光学窗口”。

其中，“近红外-II”波长在1000~1700 nm比可见光区以及“近红外-I” 存在着更高的空间分辨率、更深的穿透生物基质的深度、较低的光学吸收和散射和具有最小的组织自发荧光现象。

NIR荧光成像：

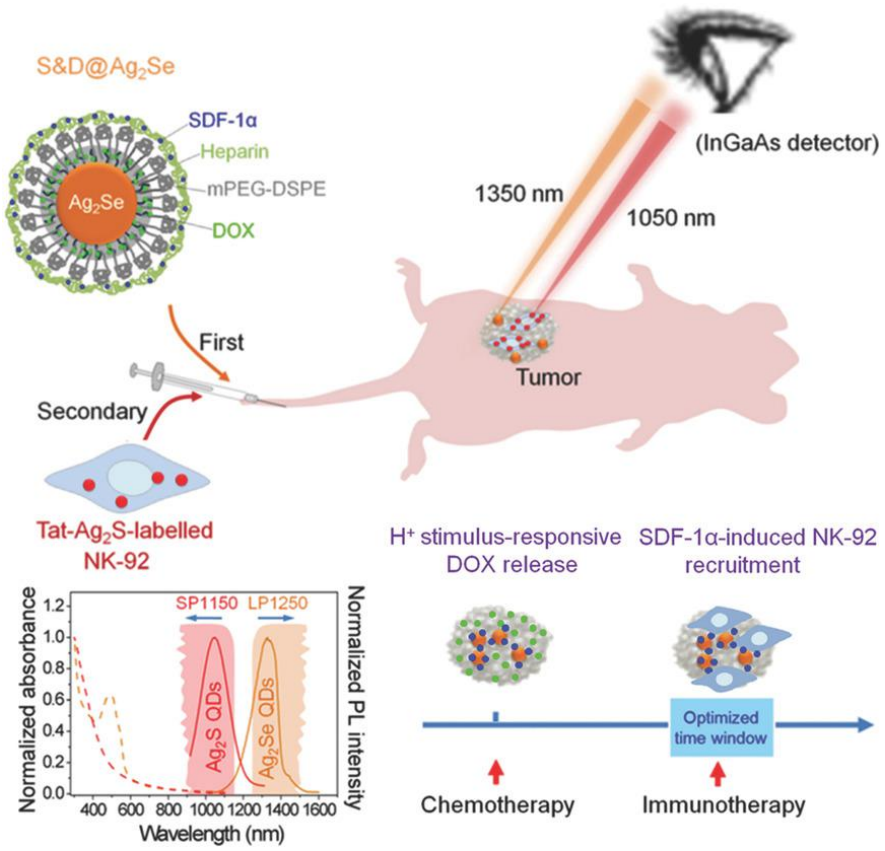


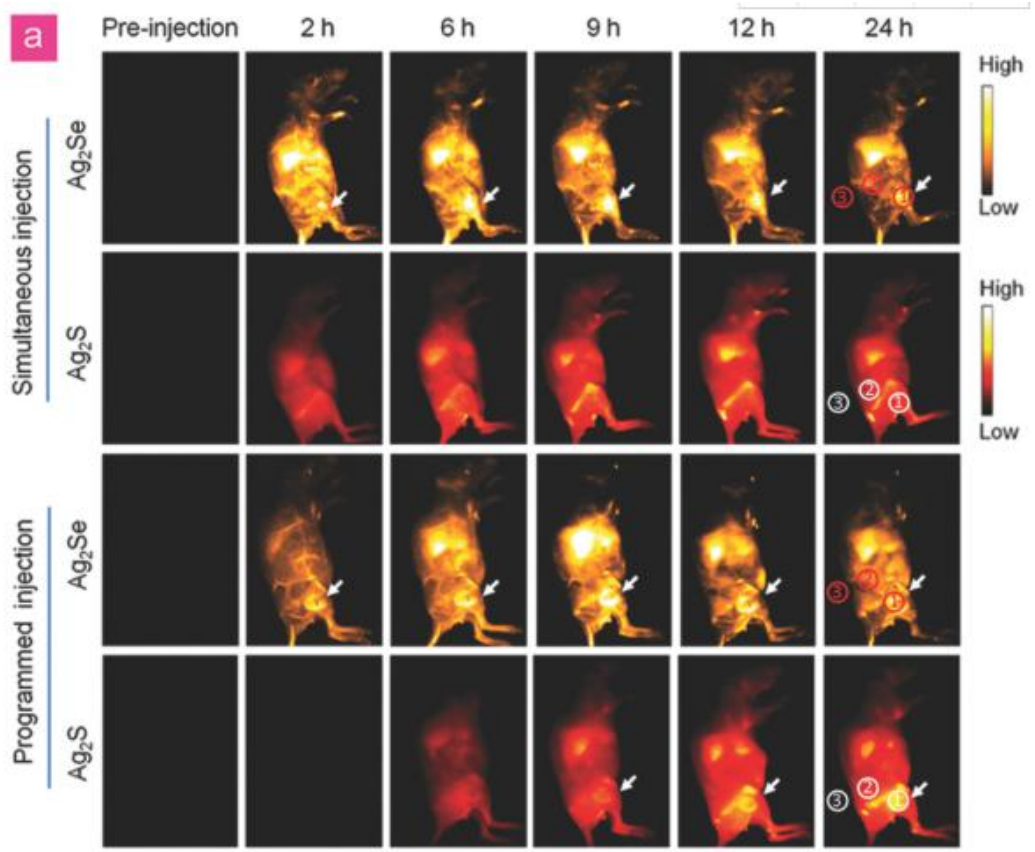


Introduction

中科院苏州纳米所王强斌研究员团队围绕“ 近红外II区活体影像技术”这一新兴领域，所取得的研究成果：

1）在国际上率先提出Ag_2S量子点体系，首次报道了其近红外II区荧光性质，并进一步拓展了Ag_2Se、Ag_2Te等量子点体系，建立了覆盖近红外II区全光谱量子点体系，实现了对活体组织原位、实时、高灵敏度和高信噪比的影像研究。





Adv. Mater. 2018, 30, 1804437

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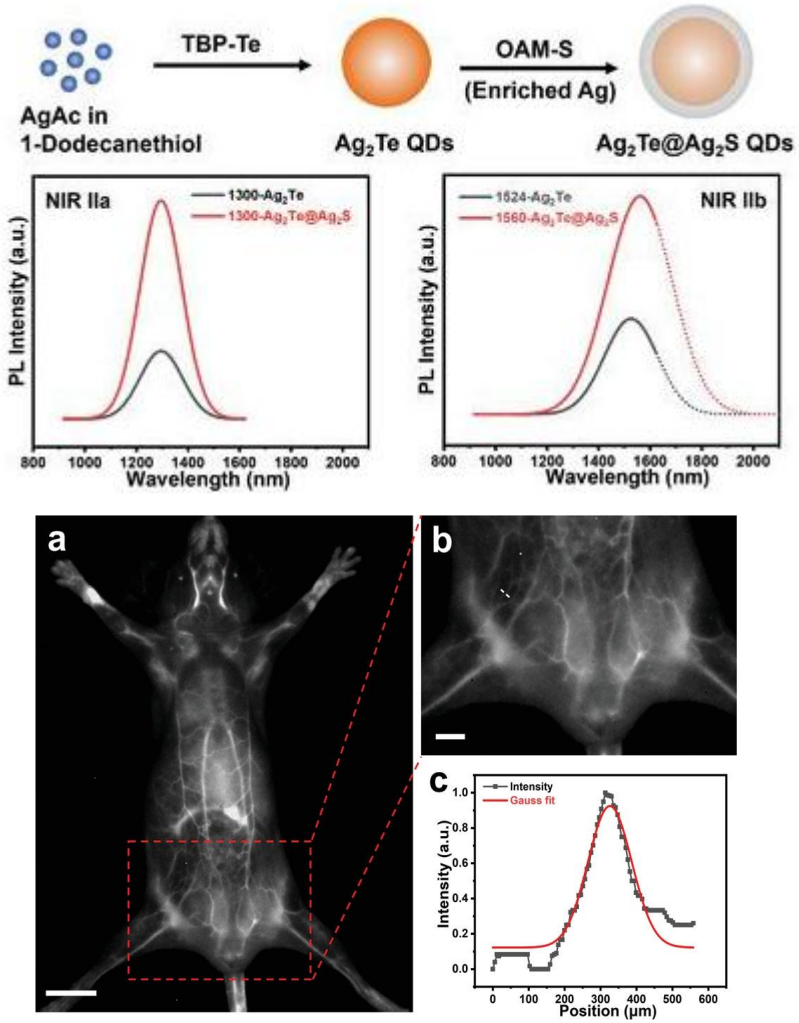
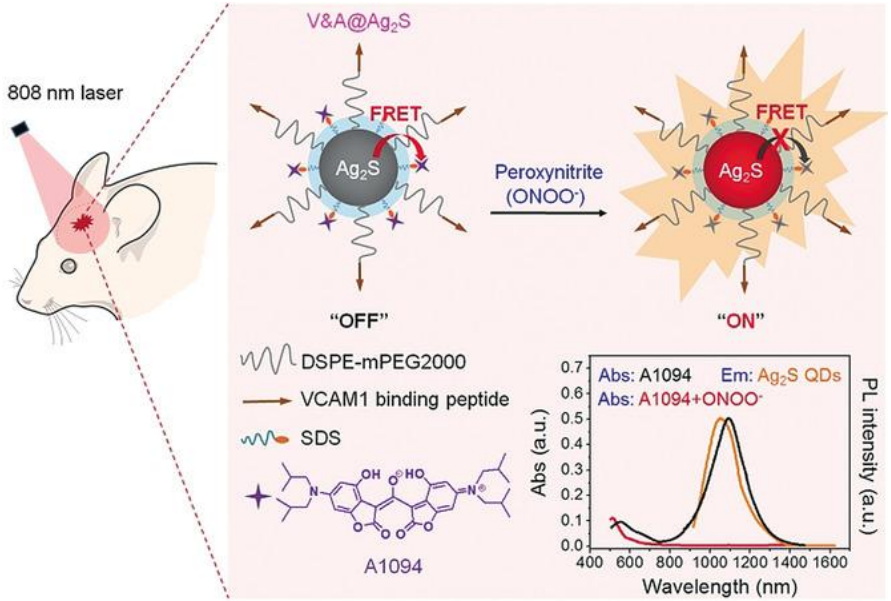
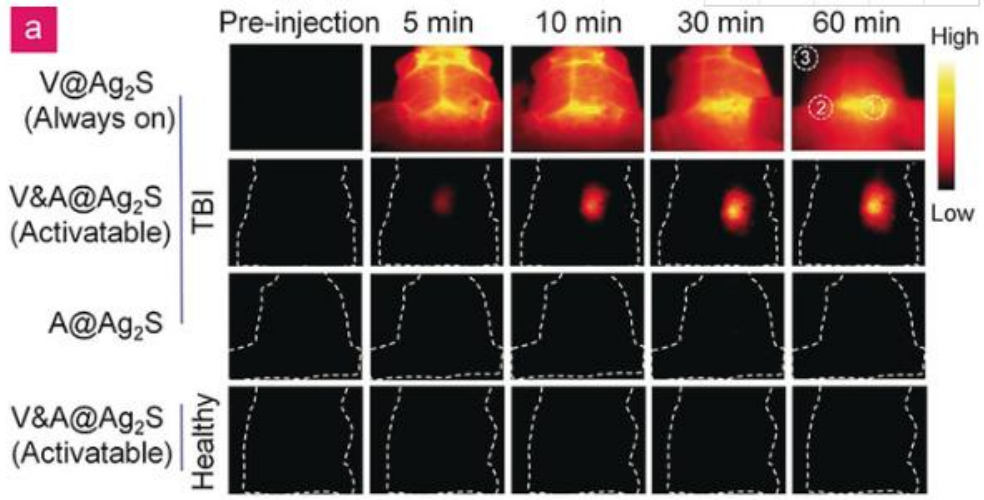


In vivo image of the whole blood vessels of a nude mouse.

Small, 2020, 16, 2001003.





Angew. Chem. Int. Ed., 2020, 59, 247-252.

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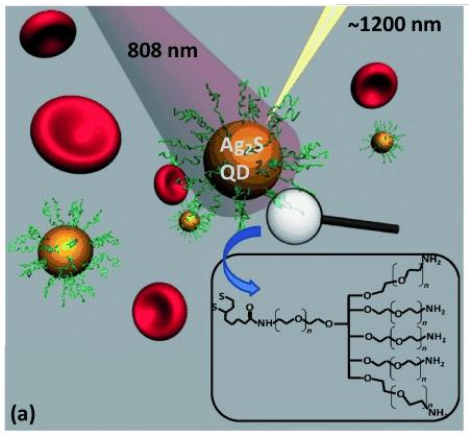
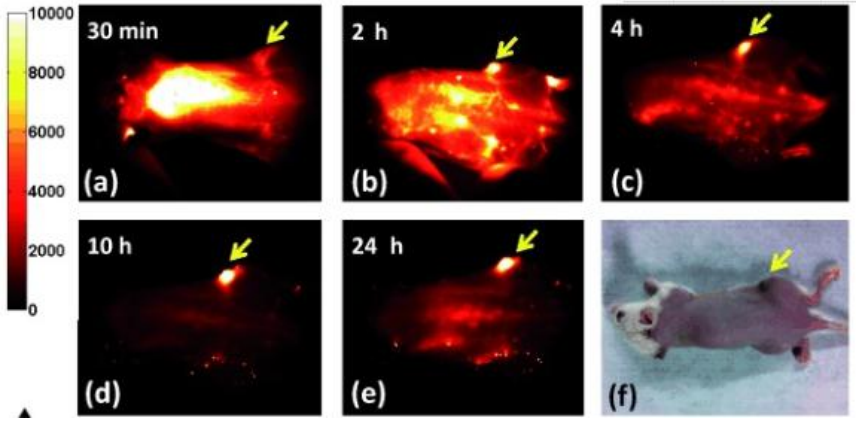
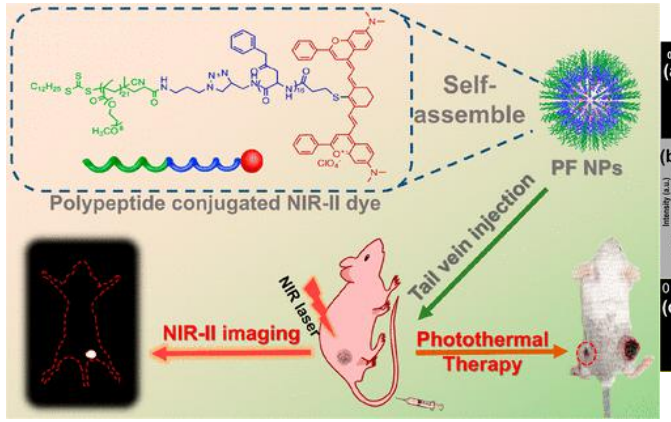
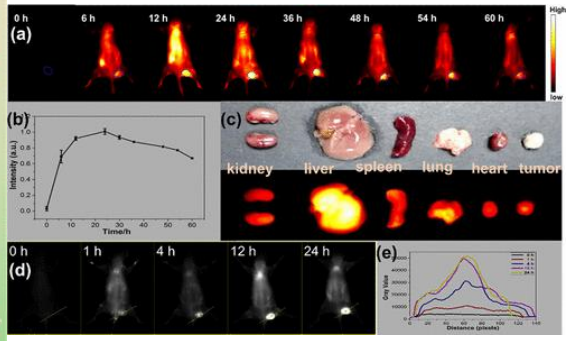
2）自主开发了基于短波红外铟镓砷（InGaAs）焦平面阵列探测器的小动物活体成像系统、兼容可见荧光成像的宽光谱（400-1700 nm）小动物活体成像系统和显微成像系统，为在分子水平、细胞层次和小动物活体模型开展跨层次、多尺度的近红外II区荧光影像研究奠定坚实基础。

3）建立了近红外II区荧光活体“可视化”生物医学研究技术平台，在小动物活体水平实现了高组织穿透深度（>1.5 cm）、高时间分辨率（~30 ms）和高空间分辨率（~25 μm）的原位、实时成像，较传统荧光成像技术实现了数量级提升；建立了针对肿瘤诊疗、药物筛选、干细胞再生医学和脑科学的精准“可视化”研究新策略。









Angew. Chem. Int. Ed. 2012, 51, 9818 –9821

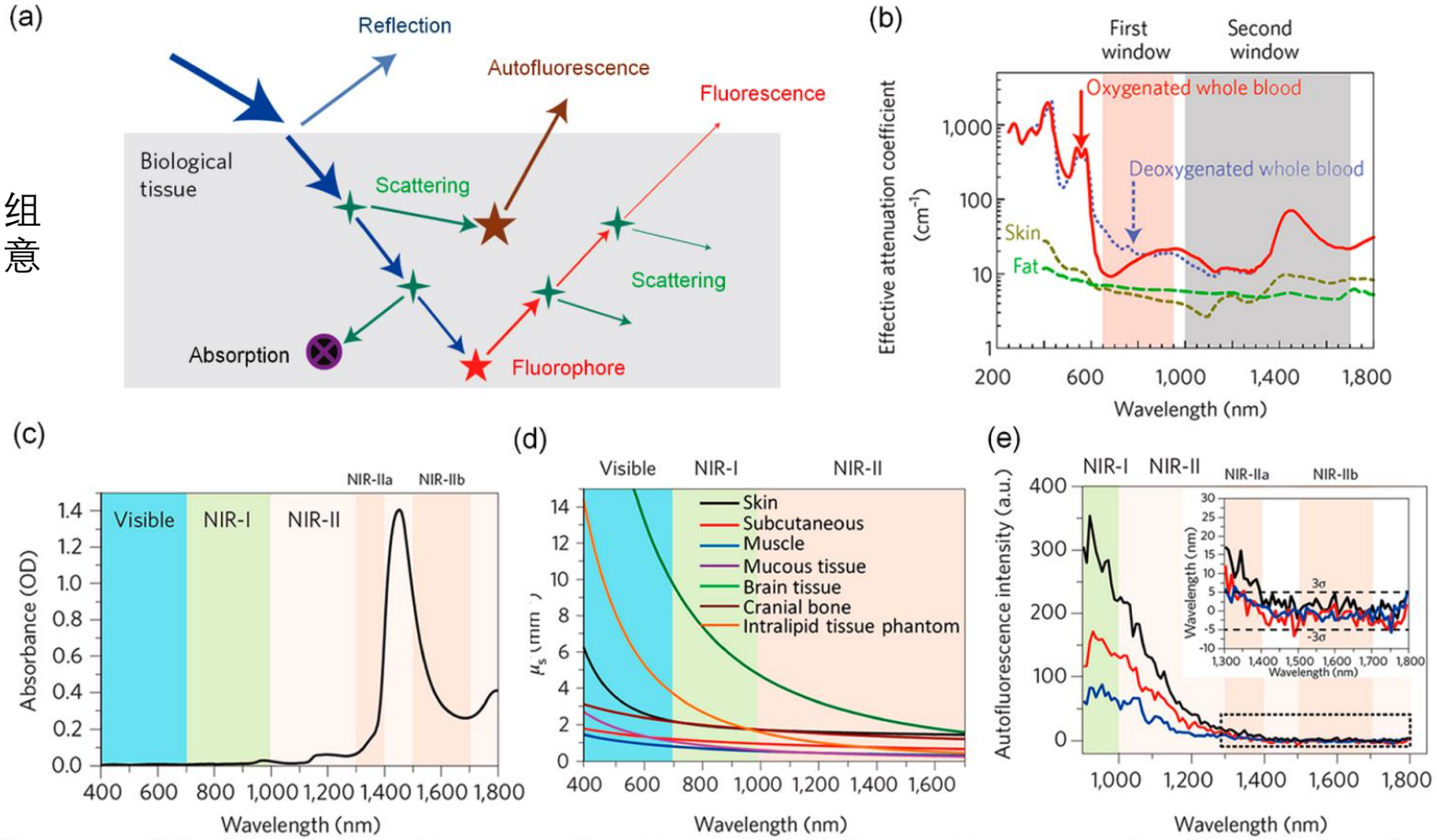
ACS Nano 2019, 13, 3691−3702

Introduction

a)荧光成像时光子与组织之间的相互作用示意图

C)水在400−1800 nm范围内的吸收光谱。

振动泛音带与组合跃迁



b)光在含氧血液、脱氧血液、皮肤和脂肪组织的有效衰减系数

d)不同生物组织在400−1700 nm范围内散射不断减小

e)解剖后的小鼠肝脏(黑色)、脾脏(红色)和心脏组织(蓝色)在808 nm激发下的自体荧光光谱。当波长大于1500 nm时几乎为零背景。

Figure 1. (a) Schematic diagram of the interactions between the photons and tissue when executing fluorescence imaging. (b) Effective attenuation coefficient of various biological components including oxygenated blood, deoxygenated blood, skin, and fatty tissue. (c) Absorption spectrum of water in the range of 400−1800 nm measured through a 1-mm-long path. (d) Reduced scattering of different biological tissues and intralipid solution in the range of 400−1700 nm. (e) Autofluorescence spectra of *ex vivo* mouse liver (black), spleen (red), and heart tissue (blue) under 808 nm excitation. Panels a, c, d, and e reproduced with permission from ref 2. Copyright 2017, Nature Publishing Group. Panel b reproduced with permission from ref 6. Copyright 2009, Nature Publishing Group.

Introduction

半导体聚合物的纳米颗粒

单壁碳纳米管　量子点　稀土掺杂纳米颗粒　小分子染料　聚集诱导发光材料

NIR-II荧光成像技术主要里程碑的时间表

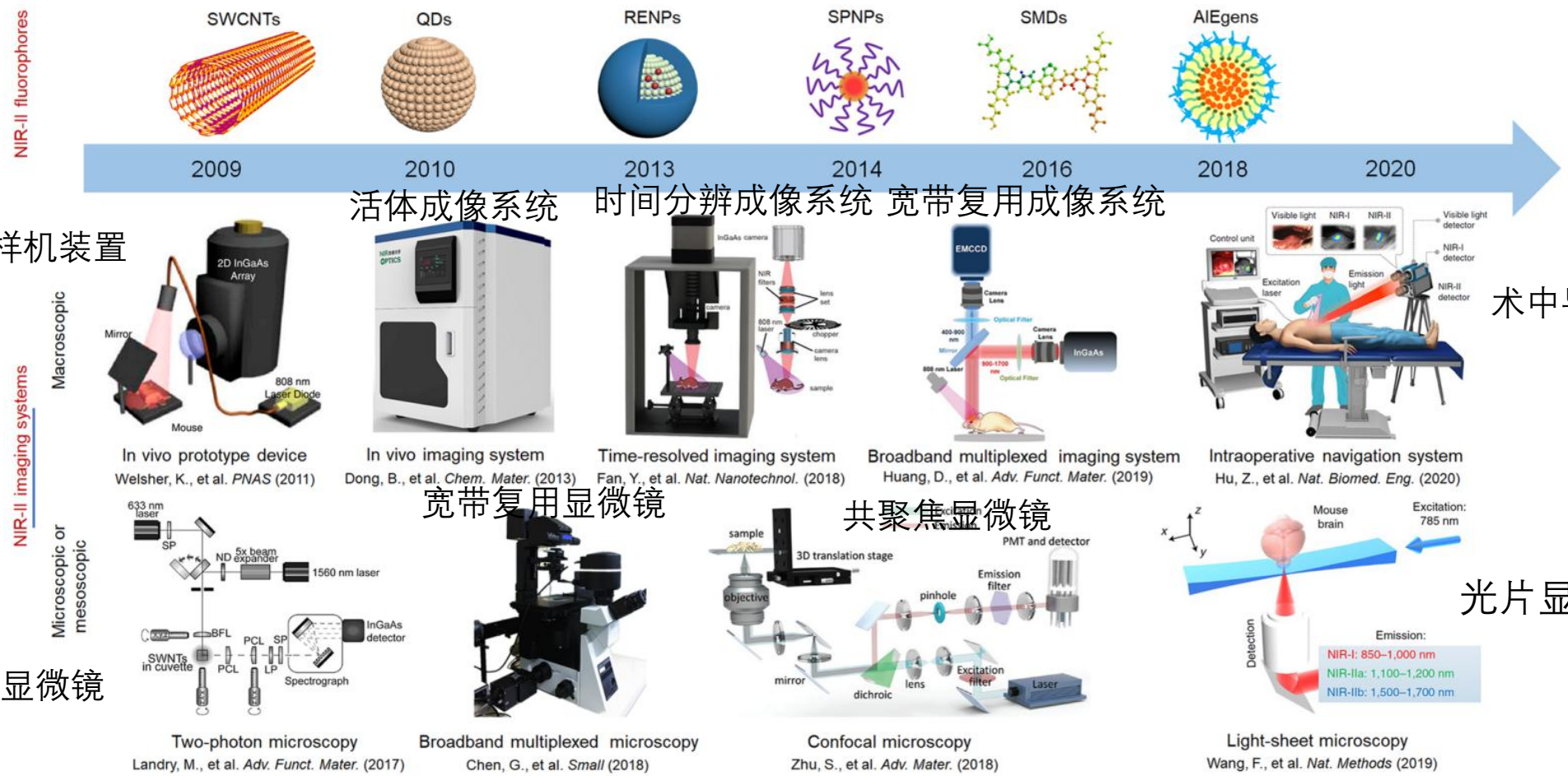


Figure 2. Timeline of major milestones in NIR-II fluorescence imaging technology. Reproduced with permission from ref 22. Copyright 2011, National Academy of Sciences. Reproduced with permission from ref 57. Copyright 2019, Wiley-VCH. Reproduced with permission from ref 58. Copyright 2018, Nature Publishing Group. Reproduced with permission from ref 59. Copyright 2020, Nature Publishing Group. Reproduced with permission from ref 60. Copyright 2017, Wiley-VCH. Reproduced with permission from ref 61. Copyright 2018, Wiley-VCH. Reproduced with permission from ref 62. Copyright 2019, Nature Publishing Group.

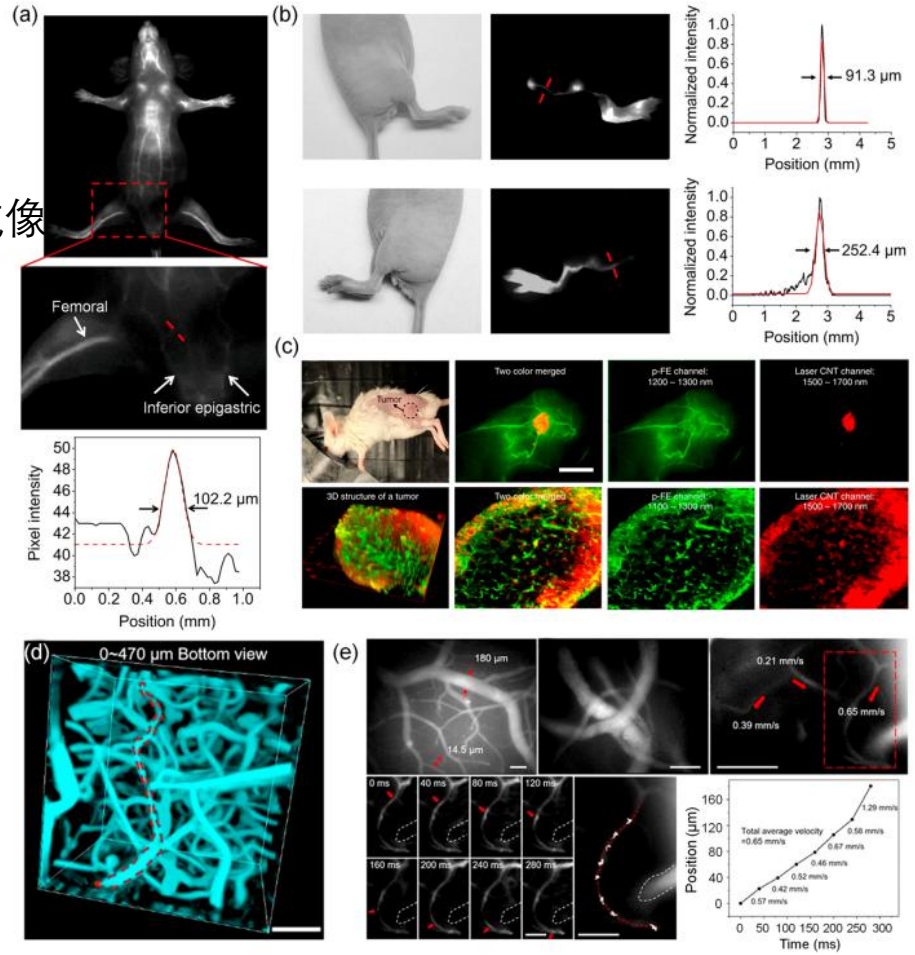
Introduction

NIR-II荧光成像技术在生物医学中的应用进展

结构成像

a)裸鼠全身血池成像

b)体内淋巴显像



c)肿瘤血管和肿瘤组织的双色荧光成像

d)恒河猴脑血管的三维共聚焦图像

e)恒河猴的血流速度活体成像

Figure 3. Structural and functional imaging using NIR-II emitting fluorophores. (a) Whole-body blood pool imaging of the nude mouse using NIR-II emitting Ag_2S QDs. (b) Comparative study of Ag_2S QDs (1200 nm, NIR-II) (upper) and ICG (835 nm, NIR-I) (below) for *in vivo* lymphatic imaging. (c) Two-color fluorescence imaging of tumor vasculatures and tumor tissues in the NIR-II window. p-EF channel: tumor vasculatures; CNT channel: tumor. (d) A 3D confocal image of cerebral blood vessels of the rhesus macaque. Bars: 100 μm. (e) *In vivo* imaging of blood flow velocities of the rhesus macaque using a wide-field NIR-II microscopy. Panels a and b reproduced with permission from ref 65. Copyright 2014, Elsevier Inc. Panel c reproduced with permission from ref 72. Copyright 2018, Nature Publishing Group. Panels d and e reproduced with permission from ref 68. Copyright 2020, Theranostics.

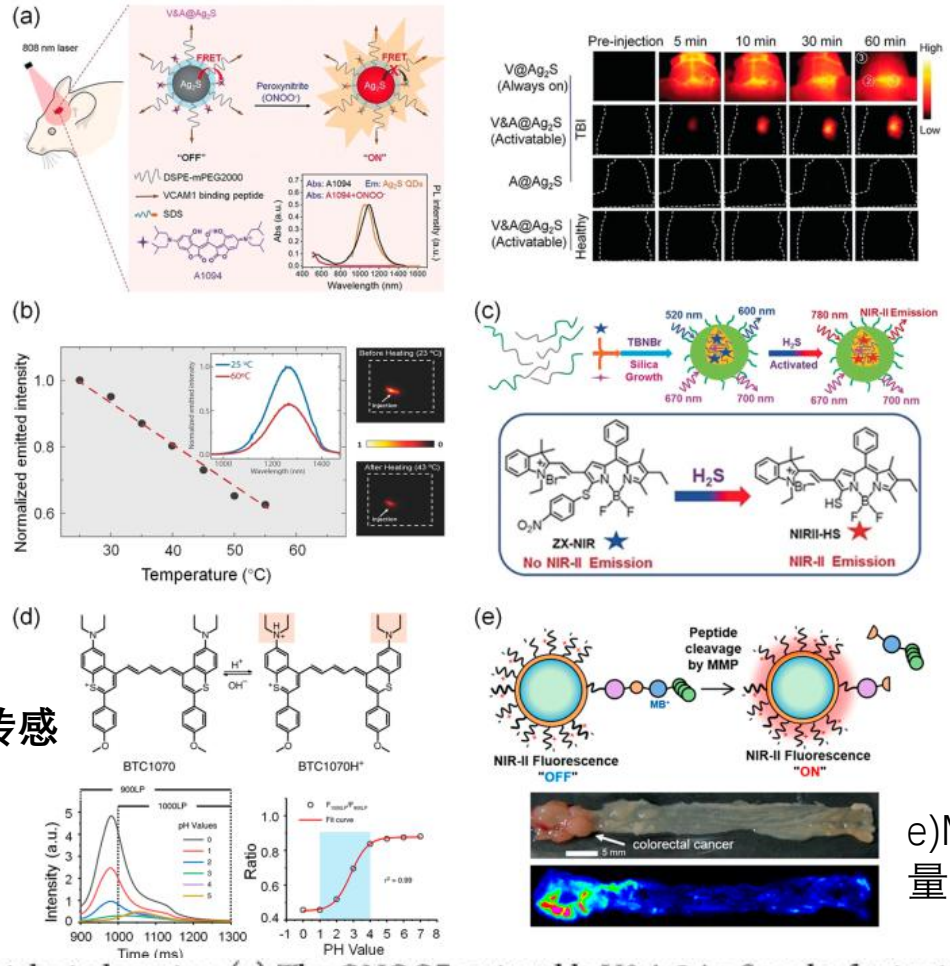
Introduction

功能成像

a)$ONOO^-$可激活的V&A@Ag_2S探针，用于**活体检测创伤性脑损伤**

b)**Temperature sensing** by a core/shell/shell PbS/CdS/ZnS QD emitting in the NIR-II window (1270 nm)

d)五甲基菁荧光团(BTCs)的**pH传感**



c)H_2S激活的**比率荧光纳米探针**

e)MMP激活的PBS/CdS/ZnS核/壳/壳量子点，**用于检测结直肠肿瘤**

Figure 4. Activatable NIR-II probes for biological sensing. (a) The $ONOO^-$-activatable V&A@Ag_2S probe for *in vivo* detection of traumatic brain injury. (b) Temperature sensing by a core/shell/shell PbS/CdS/ZnS QD emitting in the NIR-II window (1270 nm). (c) pH sensing by pentamethine cyanine fluorophores (BTCs). (d) A H_2S-activated ratiometric fluorescence nanoprobes containing a H_2S-activable boron-dipyrromethene (ZX-NIR) dye and an aza-BODIPY (aza-BOD) dye. (e) The MMP-activatable PbS/CdS/ZnS core/shell/shell QDs for colorectal tumor detection. Panel a reproduced with permission from ref 88. Copyright 2020, Wiley-VCH. Panel b reproduced with permission from ref 90. Copyright 2015, Wiley-VCH. Panel c reproduced with permission from ref 91. Copyright 2018, Wiley-VCH. Panel d reproduced with permission from ref 93. Copyright 2019, Nature Publishing Group. Panel e reproduced with permission from ref 94. Copyright 2017, American Chemical Society.

Introduction

NIR-II成像引导的治疗应用

a)**体内追踪**Ag_2S QD标记的**干细胞**用于急性肝功能衰竭小鼠的肝再生。

c)肿瘤微环境激活的NIR-II纳米热疗系统(FEAD1)，用于**精确监测、诊断和治疗腹膜转移的药物释放**。

d)在可见光和NIR-I/II窗口中由多光谱光学成像**引导的人体肝脏肿瘤手术**

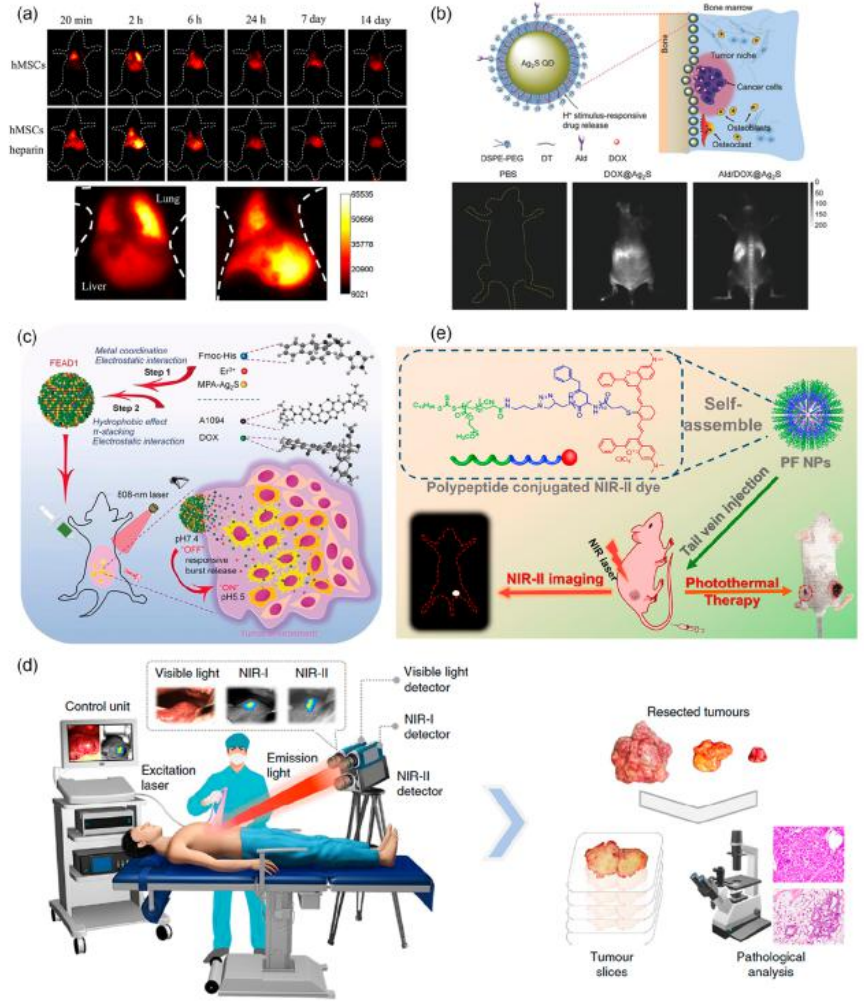


Figure 5. NIR-II imaging-guided therapy. (a) *In vivo* tracking of Ag_2S QD-labeled stem cells for liver regeneration in a mouse with acute liver failure. (b) NIR-II imaging-guided bone-targeted delivery of Ald/DOX@Ag_2S nanodrugs for bone tumor therapy. (c) A tumor microenvironment-activated NIR-II nanotheranostic system (FEAD1) for precise drug release monitoring, diagnosis, and treatment of peritoneal metastases. (d) In-human liver-tumor surgery guided by multispectral optical imaging in the visible and NIR-I/II windows. (e) NIR-II imaging-guided PTT for mammary carcinoma tumor treatment using a macromolecular fluorophore (PF) agent. Panel a reproduced with permission from ref 99. Copyright 2014, Wiley-VCH. Panel b reproduced with permission from ref 105. Copyright 2017, Wiley-VCH. Panel c reproduced with permission from ref 106. Copyright 2020, Wiley-VCH. Panel d reproduced with permission from ref 59. Copyright 2020, Nature Publishing Group. Panel e reproduced with permission from ref 114. Copyright 2019, Wiley-VCH.

b)NIR-II成像用于骨肿瘤治疗的Ald/DOX@Ag_2S纳米微球**的引导骨靶向递送**。

e)NIR-II成像引导下的PTT，用于使用大分子荧光团(PF)试剂**治疗乳腺癌肿瘤**

Introduction

光学性能：进一步提高QY。同时，提高化学稳定性和抗光漂白、抗闪烁的辐照稳定性。

功能化：通过合适的策略来引入功能成分以提高探针的水溶性和靶向性。

良好的生物相容性：应努力确保探针的毒性小

NIR-II成像在未来生物医学应用中的发展，作者提出了一些建议和展望：

NIR-II荧光团。鉴于它们的生物应用，首要的问题是**NIR-II荧光团的生物安全性**。需要满足一些重要的特性，如突出的**光学性能，易于功能化，以及良好的兼容性**。同时，还应考虑开发内源性标记的新策略。

成像系统。由于生理病理过程的复杂性和动态变化特征，需要在不同的空间和时间尺度上对其进行评价。尽管成像设备领域取得了长足的进步，但仍有许多重要的问题需要进一步解决。

(1) **NIR-II实时多通道成像系统。**由于生物体的复杂性和动态变化特性，静态的单源信号采集不能给出生理和病理变化的全貌。在这方面，传统的荧光成像受到时间分辨率和组织穿透深度的限制。**实时多通道NIR-II成像系统可以同时记录多个事件**，这可能为了解活体的奥秘和疾病的机制提供奇妙的见解。

(2) **NIR-II活体内镜成像系统。**内窥镜检查作为临床检测的标准，在检查体内空洞、中空组织和器官方面占主导地位。由于NIR-II区域的背景信号非常低，当波长大于1500 nm时，背景信号几乎为零，因此**NIR-II内窥镜可以实现传统内窥镜无法实现的超高灵敏度检测**。

(3) **NIR-II荧光集成多模式层析成像系统。**尽管NIR-II荧光系统的开发在过去十年中取得了实质性的进展，但活体成像的一个主要限制是难以获得全面的数据。**NIR-II成像与MRI和CT等其他成像技术相结合，可以为解析复杂的解剖结构和获取活体的功能信息提供强大的工具。**

Introduction

Future Applications：

(1)对于肿瘤学研究，NIR-II成像提供了活体成像肿瘤三维结构、血管分布、血流和免疫细胞动态浸润过程的可能性。然而，**基于外源性NIR-II探针的成像只能提供瞬时信息，无法实现对整个肿瘤发展过程的连续跟踪**。进一步**发展多种内源性和外源性NIR-II探针相结合的多光谱成像方法**，将为全面分析肿瘤的发生、发展和转移提供独特的工具，从而为肿瘤的精确诊断和治疗提供理论依据。

(2)在再生医学领域，**无创近红外成像**也将在探索胚胎和器官发育过程、干细胞的谱系和命运等基本生物学问题上发挥重要作用。

(3) **近红外成像在神经科学研究中也具有广阔的应用前景**。例如，**膜电位敏感的NIR-II探针**的进一步发展可能提供同时监测深部组织中大量神经细胞群体的神经活动的可能性，时间分辨率为亚毫秒，空间分辨率为亚细胞。此外，开发**可激活的NIR-II探针，可以特异性地检测离子和神经递质，如K^+，Ca^{2+}和多巴胺**，将极大地促进对神经活动化学机制的研究。

(4)近红外成像最具临床应用前景的是**图像引导下的肿瘤手术**。在未来，先进的NIR-II成像技术可能会大大提高肿瘤手术的精度。