Literature Report

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Perspective

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Development of Photoacoustic Probes for *in Vivo* Molecular Imaging

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个人简介

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研究领域 **Photoacoustic Imaging; Infectious Diseases; Neurological Disorders**

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Introduction

光声（PA）成像是一种新兴的非侵入性成像方式，涵盖了光学和超声成像的属性。由于声音在生物组织中的低散射，这种先进的方法是活体动物和人体器官的非侵入性、深层组织生物成像的理想选择(PA成像可在厘米深层组织内实现高对比度和高分辨率)，克服了荧光成像的有限成像深度。

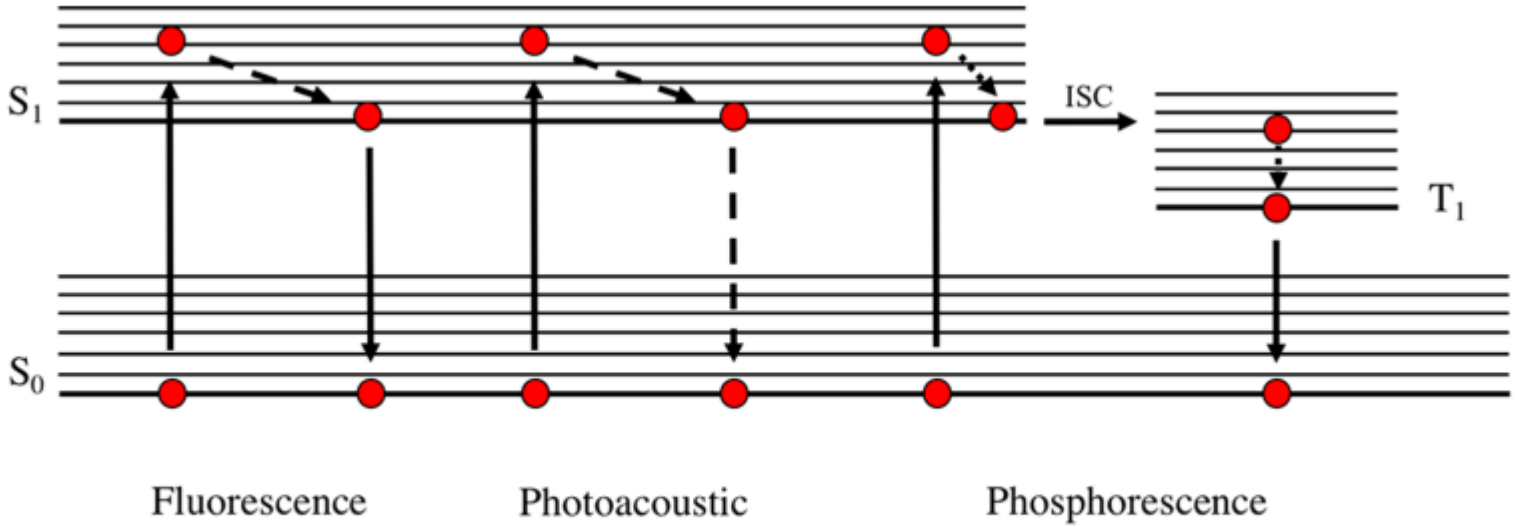


Figure 1. Stylized Jabłoński diagram depicting the origin of signals in fluorescence, photoacoustic, and phosphorescence imaging. Absorption, intersystem crossing (ISC), and emission events are indicated by solid lines, whereas nonradiative processes are depicted by dashed lines.

从理论上讲，任何吸收光的材料都可以产生PA信号。用光照射光吸收体会产生激发态，这种激发态可以通过辐射发射或非辐射衰变返回到基态。在无辐射弛豫的情况下，光吸收体以热的形式释放能量，从而提高局部温度。温度的快速升高导致热弹性膨胀，并产生压力变化。通过脉冲激发源，可以产生波动的(兆赫)压力波，这些压力波以声波的形式在介质中传播。一组超声转换传感器将检测到的声音转换成电信号，这些电信号被重建以提供三维图像.

Introduction

理想的PA探针必须在近红外NIR-I (620-950 nm)或NIR-II (1000-1700 nm)的生物窗口内具有明显的吸收能力,这样激发光可以穿透组织几厘米，同时可以使内源性物种的光学背景信号最小化。此外，具有高消光系数和低量子产率的生色团被认为是PA成像的最佳选择，因为它们吸收大量光并优先通过非辐射过程弛豫。

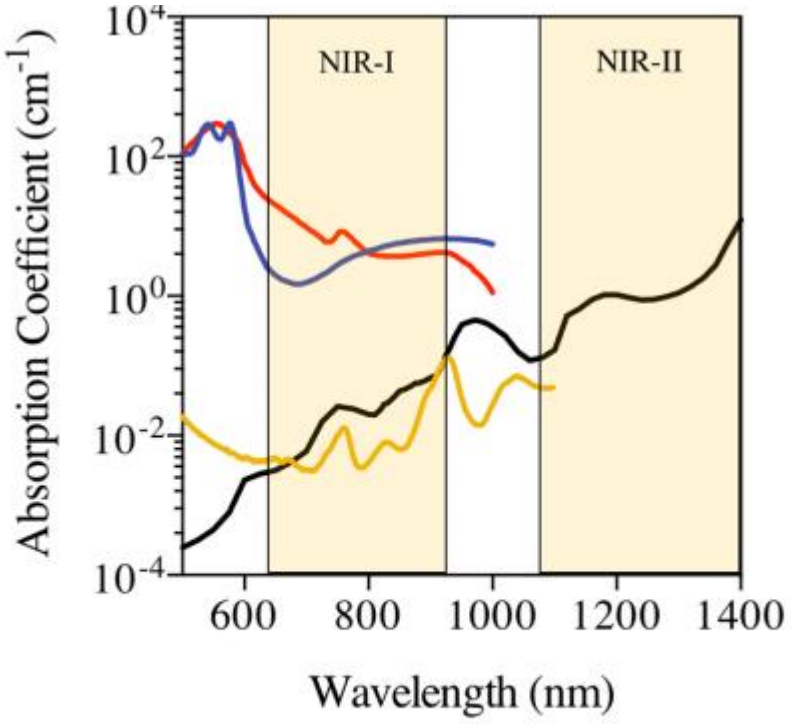


Figure 2. Absorption coefficient of biological chromophores: oxyhemoglobin (red), deoxyhemoglobin (blue), lipids (yellow),[12,13] and water (black).[14] Data from http://omlc.ogi.edu/spectra/.

PA探针设计的一个潜在策略是利用现有的近红外turn-off荧光探针，这些强荧光分子在与刺激物相互作用时发生猝灭，产生非辐射的PA活性产物。此外，其他光物理性质，如激发态吸收、弛豫动力学、光漂白和三重态的贡献，也是PA探针开发中的关键考虑因素。目前，这些都难以预测，并且需要在性能和化学结构之间建立更好的联系。满足这些特性的常见PA探针包括花菁、半花菁、氮杂-BODIPY、方酸菁和卟啉/卟啉类 (图3)。

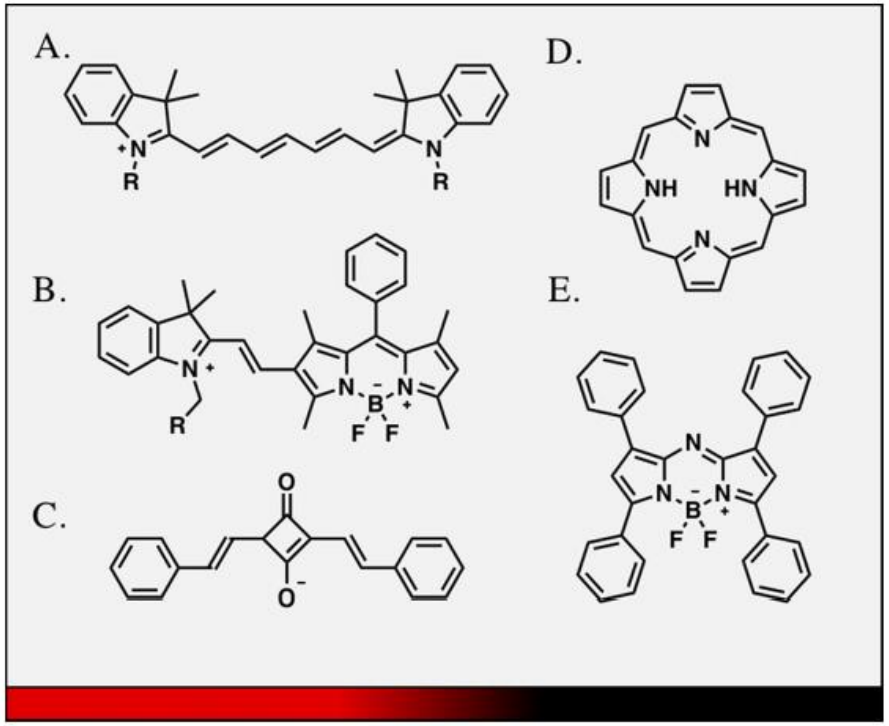


Figure 3. Representative structures for common NIR PA dye platforms: (A) cyanine, (B) semicyanine, (C) squaraine, (D) porphyrin/porphyrinoid, and (E) aza-BODIPY.

Introduction

1.基于切割的探针由两个小分子发色团组成，由基质金属蛋白酶-2(MMP-2)序列连接。该方法利用MMP-2介导的连接体的裂解来断开两个发色团。

2.基于分子间组装的PA探针利用大量的分子间相互作用（聚集、聚合和组装）在刺激物存在的情况下调节PA信号。聚集可以促进探针的荧光猝灭和PA强度增强，分子间组装方法的一个显著应用是使用聚集作为温度响应触发器。通过基于温度变化的J-聚集体形成，可以测量温度阈值，或J-聚集体损失所需的温度。

3.通过可逆结合直接检测分析物，极大地扩大了分子成像的可获得靶点的数量。基于可逆结合的检测允许对动态过程进行成像，例如，神经元放电之前、期间和之后的钙浓度变化。

4.基于反应的探针经过刺激选择性修饰以提供PA反应。不可逆和可逆方法都是可能的，然而当前的例子仅限于不可逆触发。可逆性对于动态监测很重要，而不可逆性由于产物积累可以提高灵敏度。

5.细胞的电子环境与多种生物现象（如神经元信号和心肌细胞功能）密切相关。此外，细胞极性的改变也被认为是几种病理（如癌症、神经元损伤和糖尿病)的潜在生物标志物。

到目前为止，大多数PA探针是通过消光系数，量子产率，细胞或组织定位或这些因素的组合来激活的。总体而言，可激活的PA探针主要分为五类：(1)裂解保留，(2)分子间组装，(3)可逆结合，(4)基于反应，(5)电响应 (图4)。

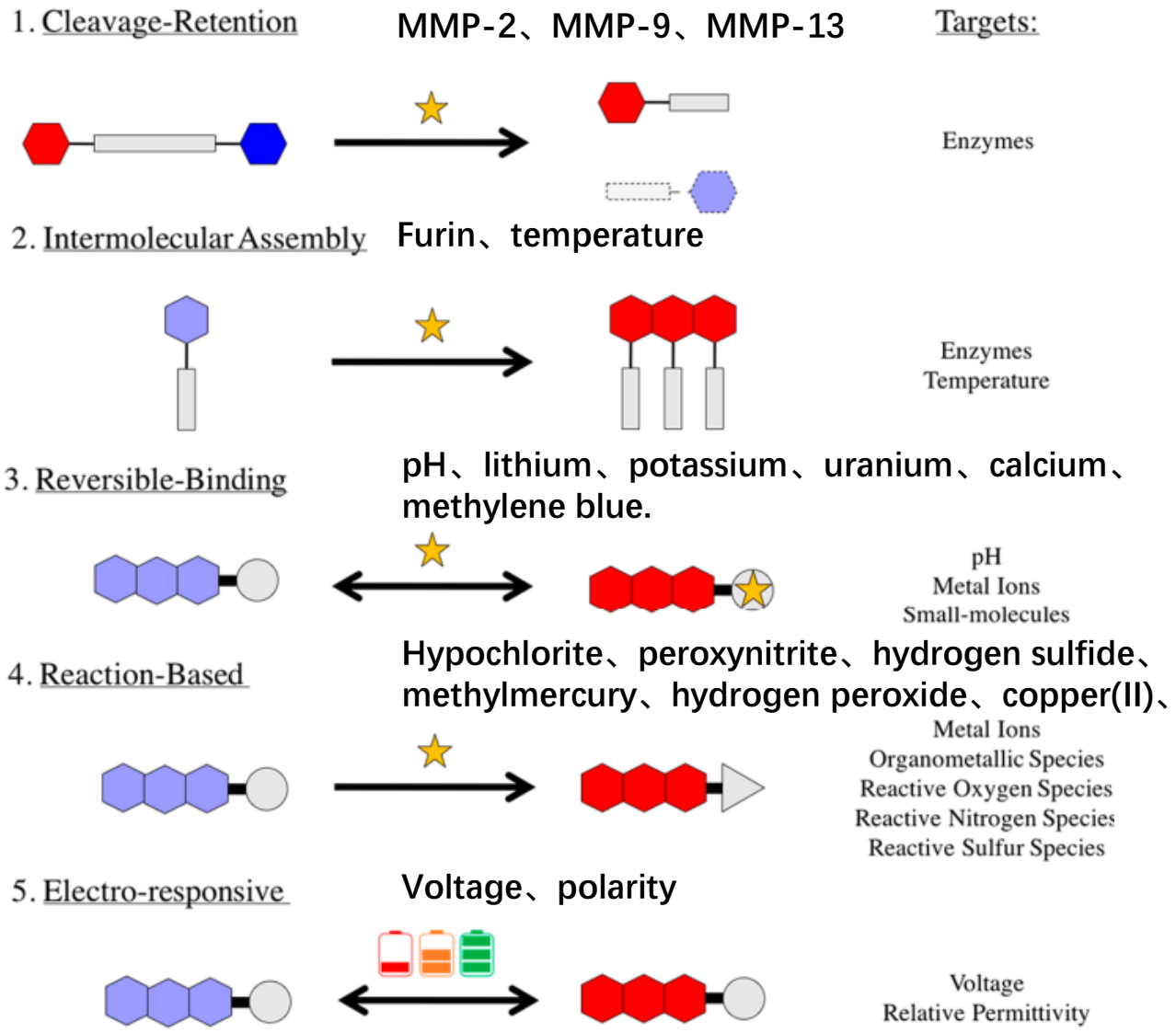
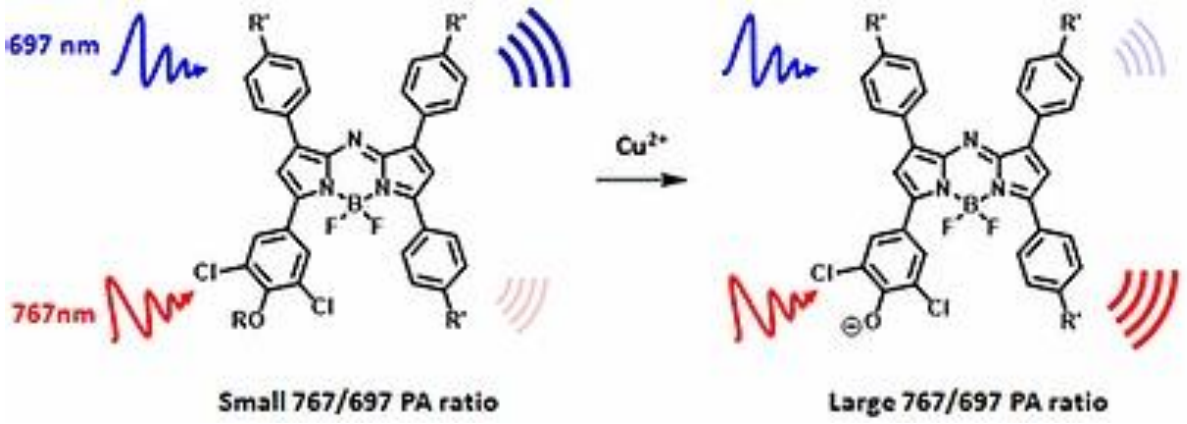


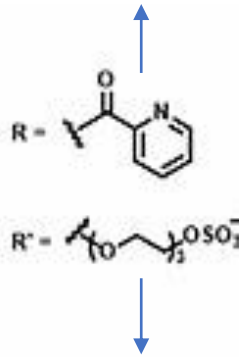
Figure 4. Schematic representations of methods for the development of activatable PA probes.

Introduction

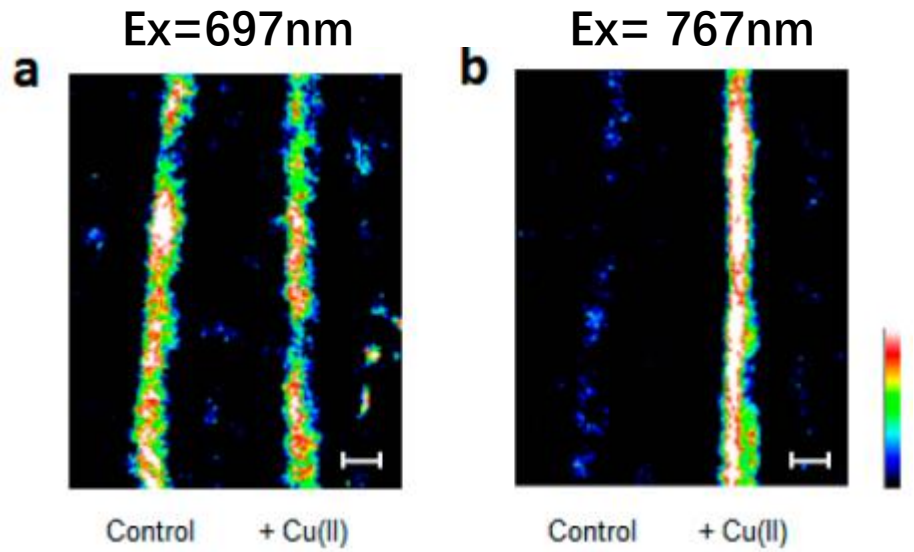
Reaction-based PA probe:



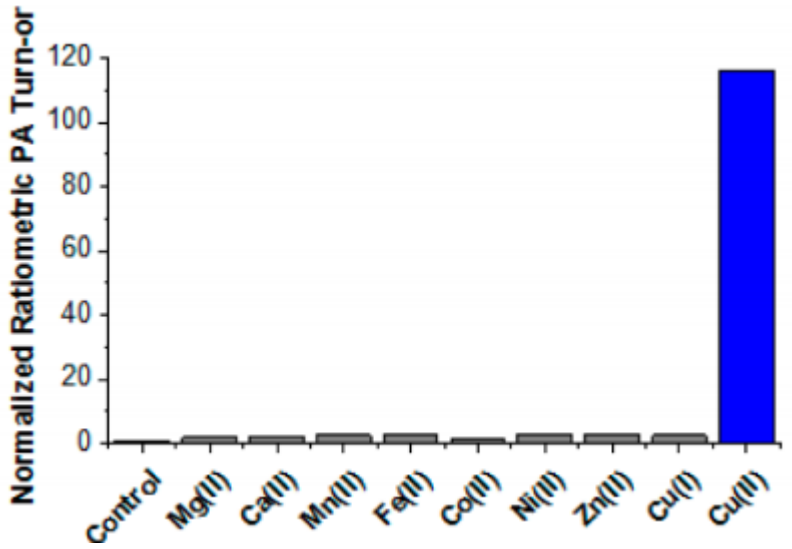
在Cu（II）存在下很容易被水解



增强水溶性



Photoacoustic images of 10 μM APC-2 (PBS + 0.1% CrEL, pH 7.4) in FEP tubing overlaid with a 1 cm thick phantom treated with 0 and 10 equiv of Cu(II)

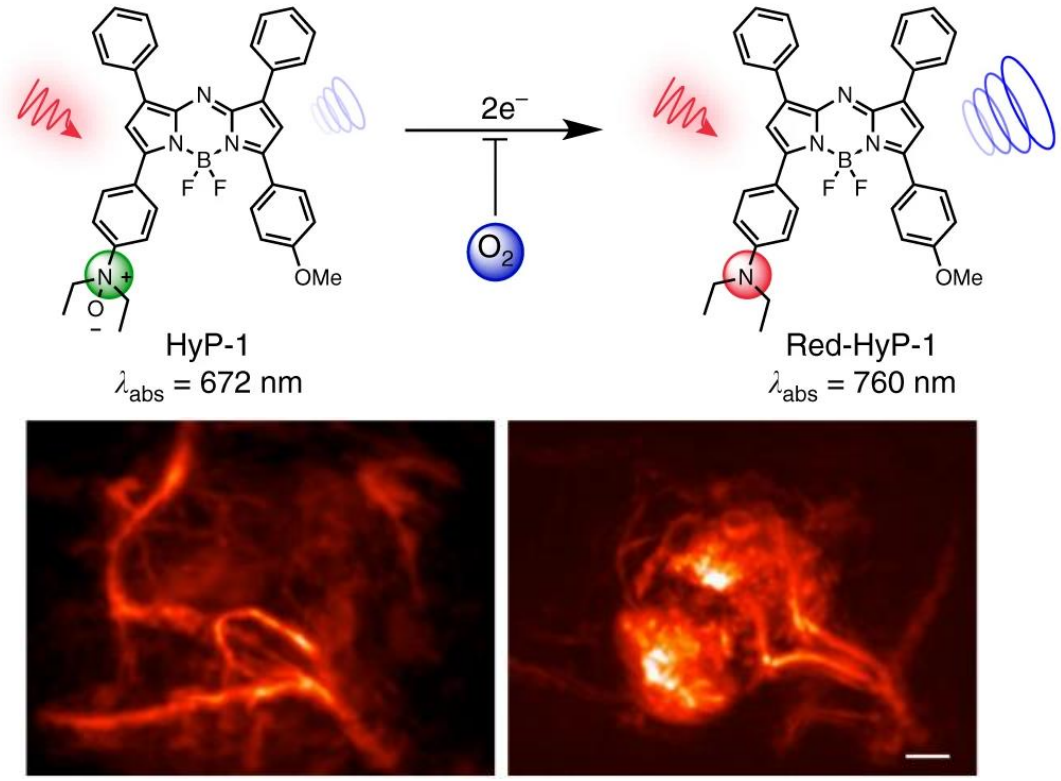


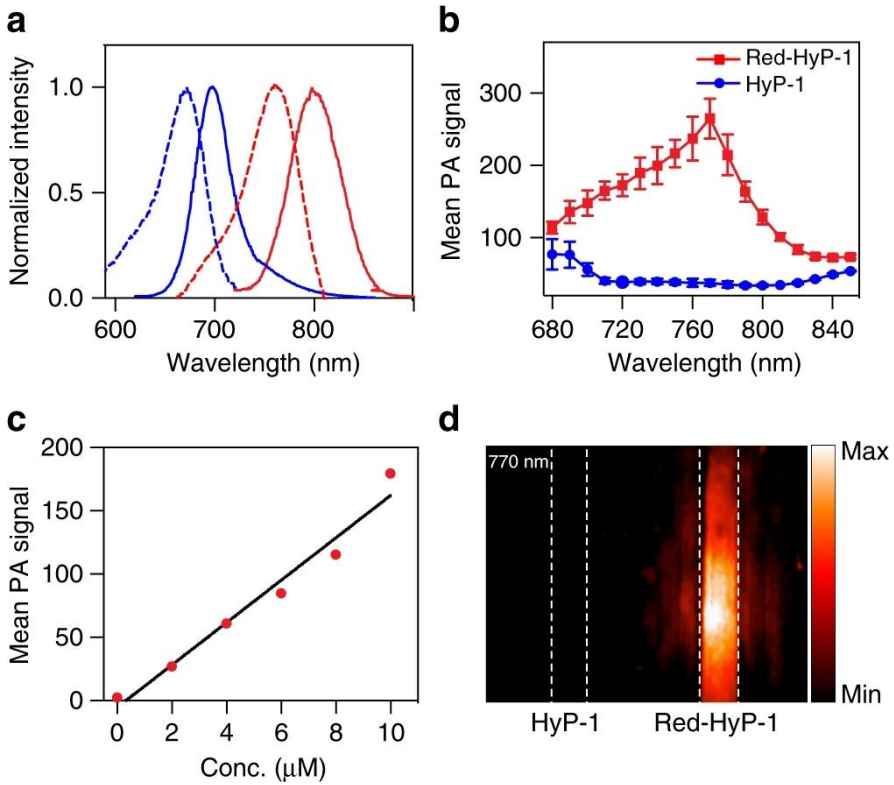
J. Am. Chem. Soc. 2015, 137, 15628-15631.

Introduction

HyP-1具有基于N氧化物的触发器，可以在缺氧的情况下进行生物还原，引起吸光度从672nm到760nm的红移变化。

Reaction-based PA probe:



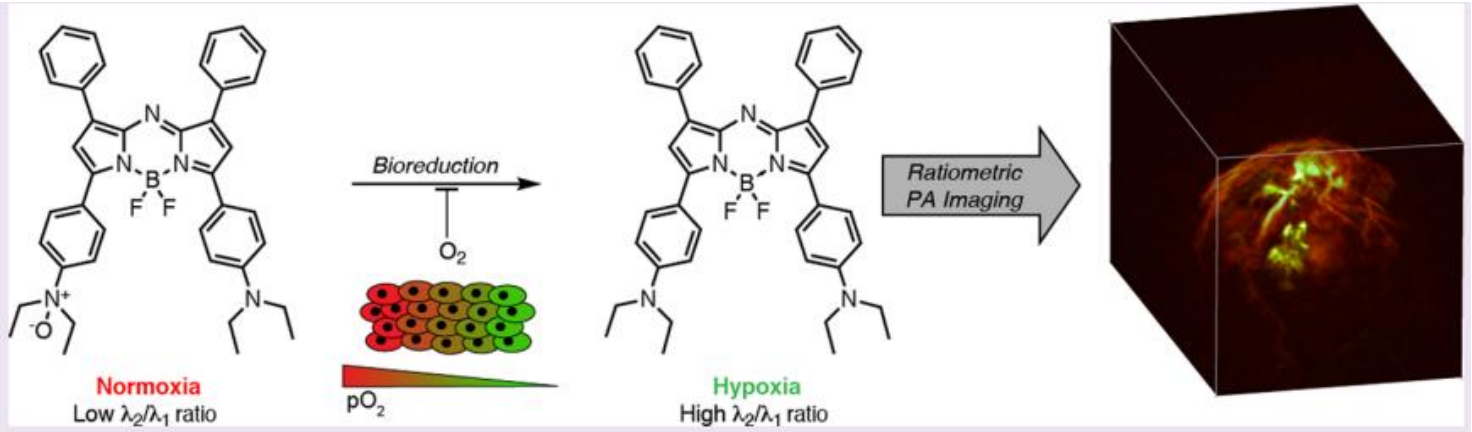


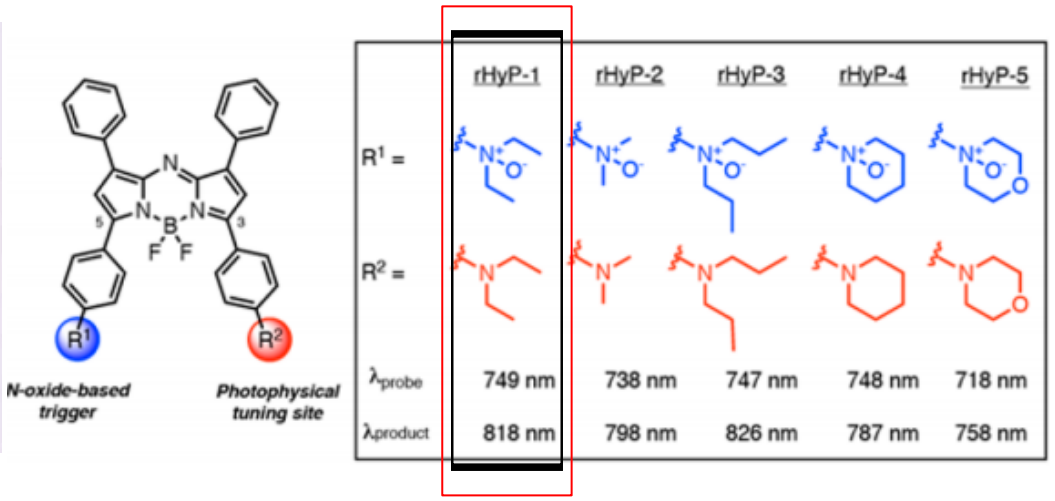
Photophysical characterization of HyP-1 and red-HyP-1. a Normalized absorbance (dashed) and emission (solid) spectra of HyP-1 (blue) and red-HyP-1 (red). b PA spectra of HyP-1 and red-HyP-1. PA images of HyP-1 and red-HyP-1 solutions (10 μM in 0.1 M potassium phosphate buffer (pH 7.4) with 50% EtOH co-solvent) in tissue-mimicking phantoms were obtained, and the mean PA signal corresponding to each compound was plotted as a function of wavelength. Results are presented as mean ± SD (n = 3). c PA signal corresponding to various concentrations of red-HyP-1. d PA image (770 nm) of HyP-1 and red-HyP-1 solutions (10 μM in 0.1 M potassium phosphate buffer with 50% EtOH co-solvent) in tissue-mimicking phantom. Dashed lines indicate positioning of FEP tubes

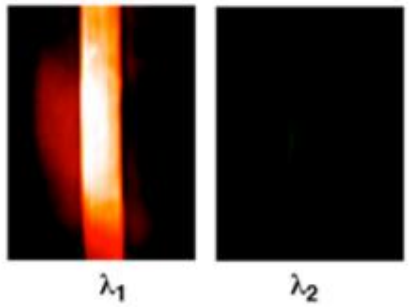
Nat. Commun. **2017**, 8, 1794-1802.

Introduction

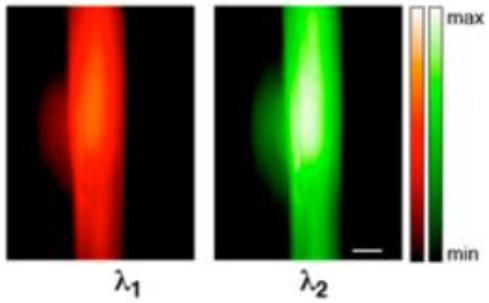
Reaction-based PA probe: 基于N氧化物触发器，在缺氧的情况下进行生物还原，引起吸光度从697nm到818nm的红移变化。







Ex=697nm Ex=818nm

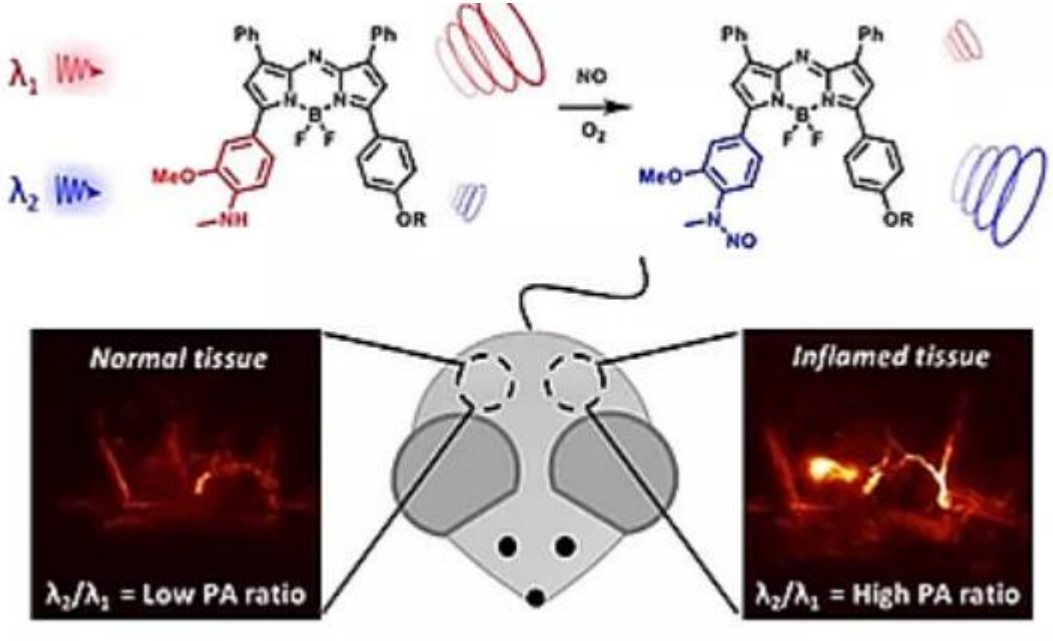


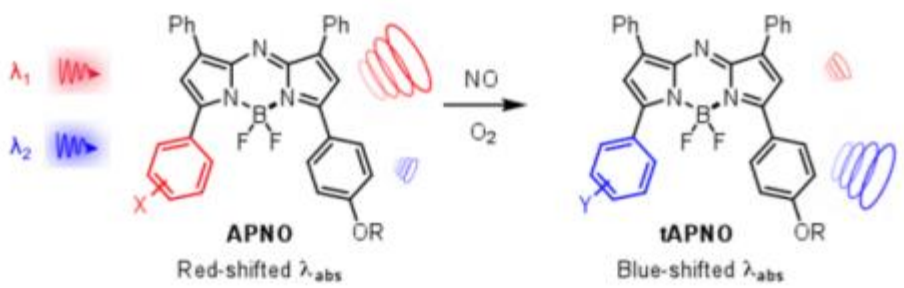
Ex=697nm Ex=818nm

ACS Chem. Biol. 2018, 13, 1838-1843.

Introduction

Reaction-based PA probe:





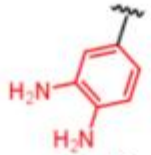
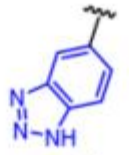
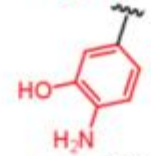
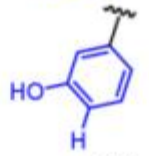
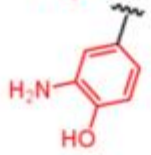
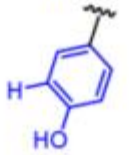
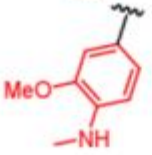
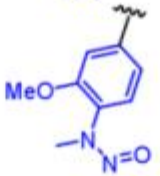
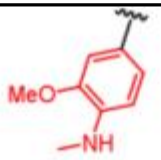
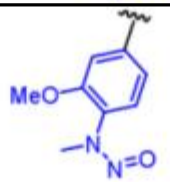
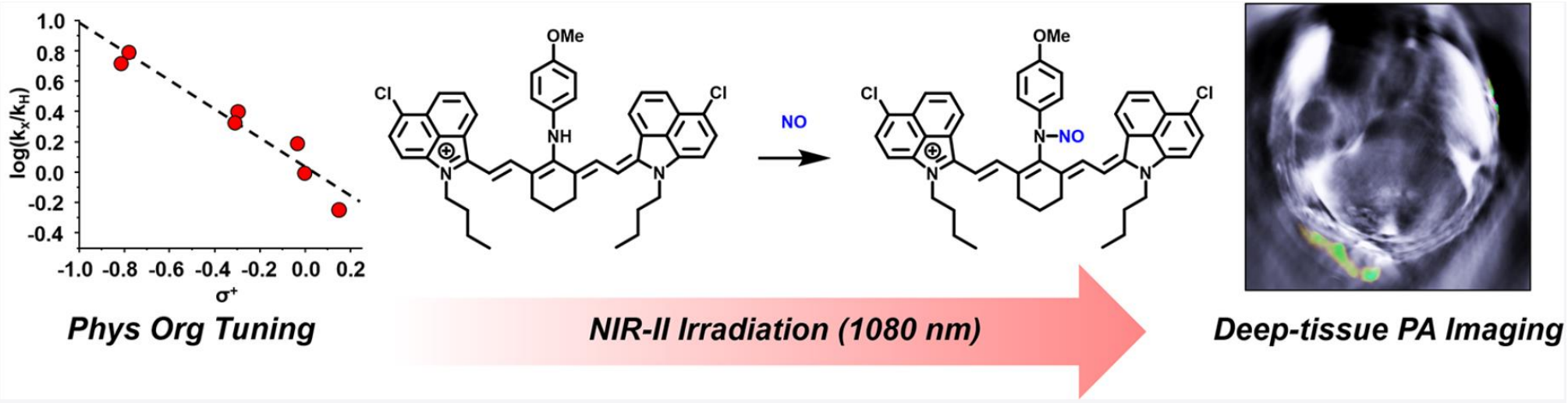
Probe	NO Trigger	NO Product	Mechanism
APNO-1 R = Me			Triazole formation
APNO-2 R = Me			Deamination
APNO-3 R = Me			Deamination
APNO-4 R = Me			*N*-nitrosation
APNO-5 R = PEG			*N*-nitrosation

Figure 1. Structures, triggers, and sensing mechanisms for the panel of APNO (red) and tAPNO (blue).

J. Am. Chem. Soc. 2018, 140, 1011-1018.

Introduction



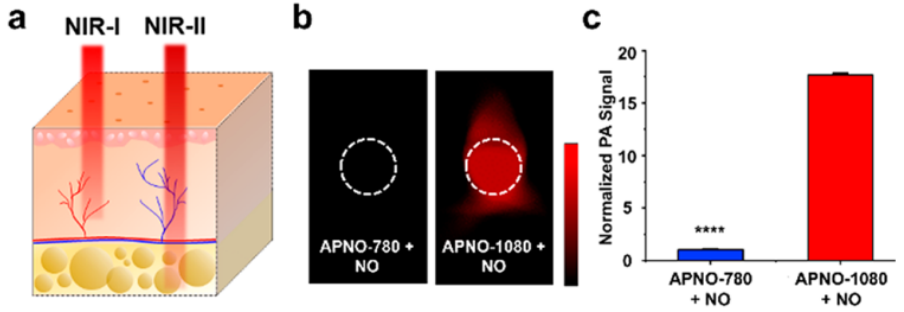


Figure 3. (a) Schematic illustrating that NIR-II light can penetrate deeper into tissue compared to NIR-I light. (b) Representative PA images of APNO-780 and APNO-1080 (10 μM) treated with NO and overlaid with a 3 cm thick tissue imaging phantom. (c) Quantified data from (b). Error bars = SD (n = 3) Statistical analysis was performed using a two-tailed Student's t test (α = 0.05). ****: p < 0.0001.

https://doi.org/10.1021/jacs.1c03004
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX