谈谈简单的生物材料，聊聊实验之外的不简单

李团伟

中国科学技术大学

2017.9.27

目录

一、实验室概况介绍 • 实验室成员

BOSS：闫立峰教授

中国科学技术大学-化学物理系 http://dcp.ustc.edu.cn/szdw/xszb/ylf/201312/t20131209_179225.html

中国科大研招宣讲系列-闫立峰http://v.youku.com/v_show/id_XMjc4MzEzNTY3Mg==.html?spm=a2h3j.8428770.3416059.1

一、实验室概况介绍 • 课题组研究方向

躺着做试验的石墨烯

- ✓ “973”子课题：二维结构材料制备与性能
- ✓ 企业项目：石墨烯规模化低成本制备

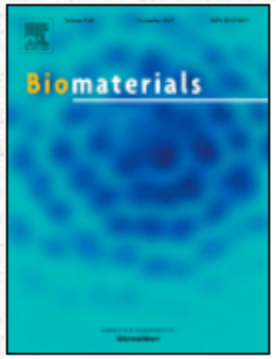
坐着做试验的生物质转化

企业项目：生物质转化制烷烃

站着做试验的生物材料

- ✓ 自修复近红外荧光与pH超敏感聚多肽纳米粒的合成及应用
- ✓ 近红外键合聚多肽高分子合成及在光动力治疗中的应用
- ✓ 生物降解近红外发光聚合物纳米粒子在药物示踪中的应用

二、生物材料 • 定义



Biomaterials

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A biomaterial is now defined as a **substance** that has been **engineered** to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any **therapeutic or diagnostic procedure.**

cancer diagnosis and therapy

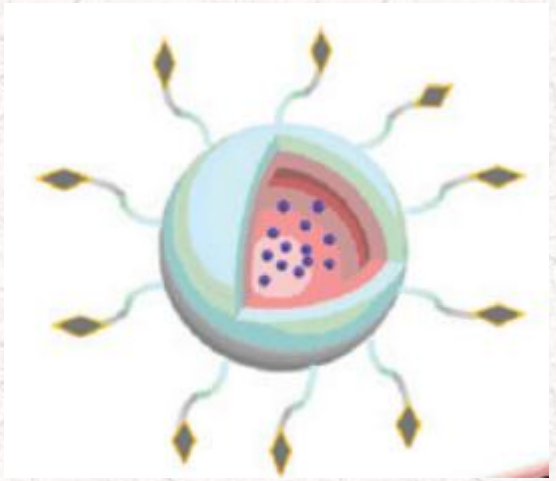
implantable devices

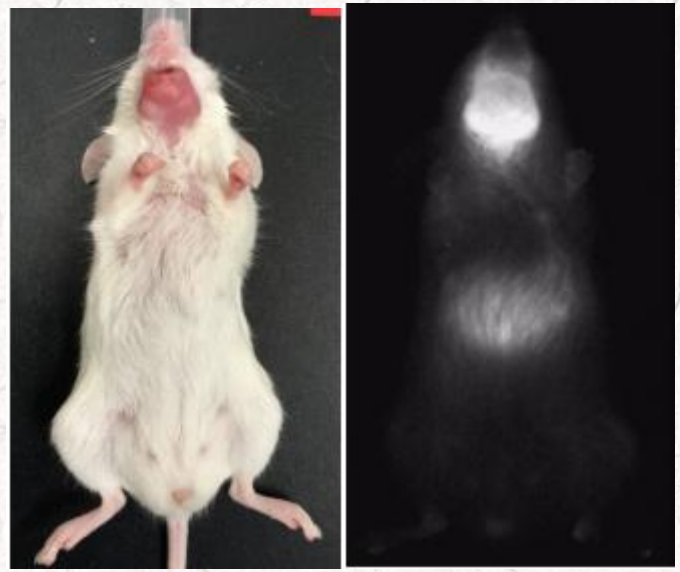
drug delivery systems

gene vectors,

bionanotechnology

tissue engineering





Biomaterials 29 (2008) 4348–4355

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Self-assembled biodegradable micellar nanoparticles of amphiphilic and cationic block copolymer for siRNA delivery

Tian-Meng Sun [a,†], Jin-Zhi Du [b,†] Li-Feng Yan [a], Hai-Quan Mao [d], Jun Wang [a,c,*]

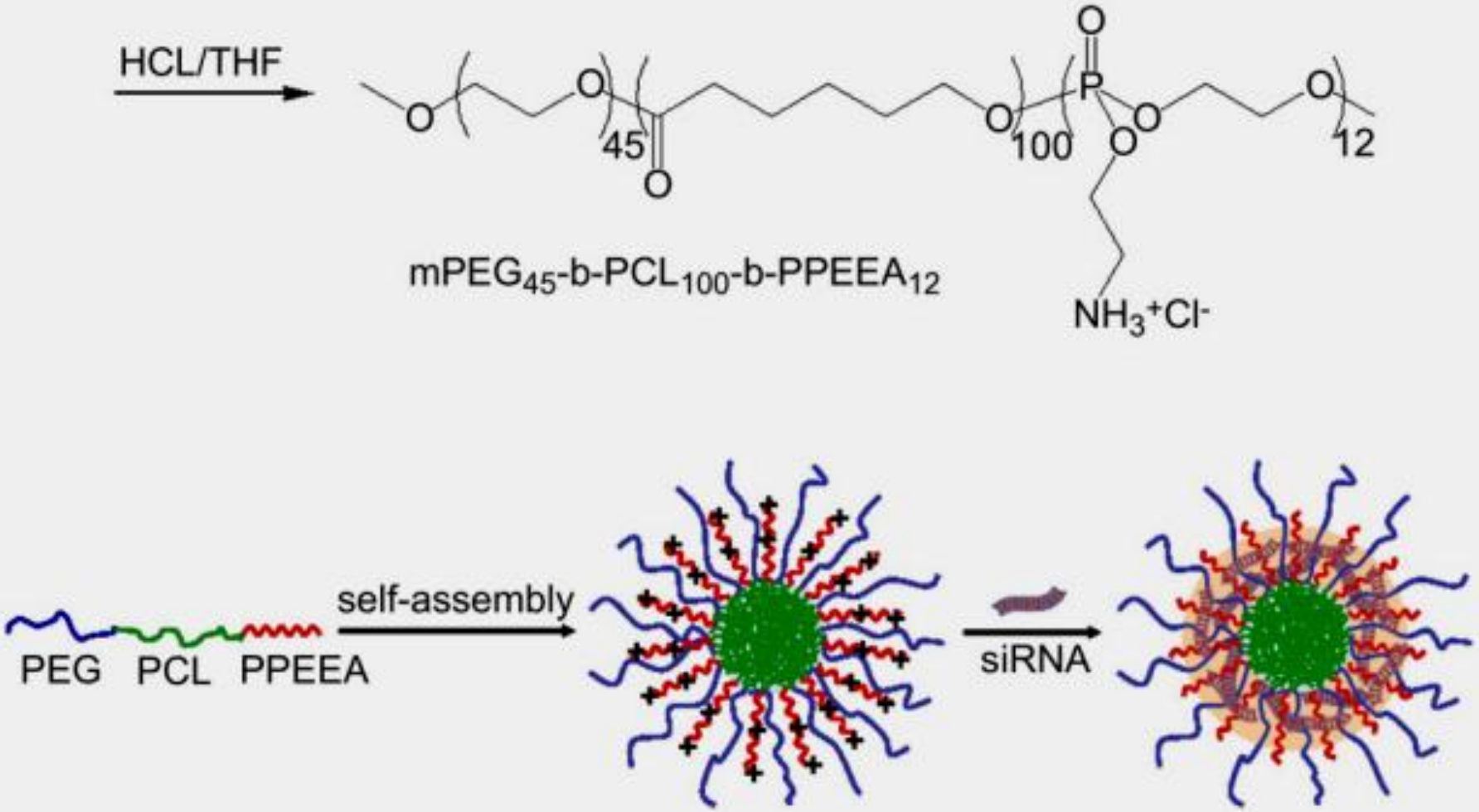
[a] Hefei National Laboratory for Physical Sciences at Microscale, University of Science and Technology of China, Hefei, Anhui 230027, PR China
[b] Department of Polymer Science and Engineering, University of Science and Technology of China, Hefei, Anhui 230026, PR China
[c] School of Life Sciences, University of Science and Technology of China, Hefei, Anhui 230027, PR China
[d] Department of Materials Science and Engineering, Johns Hopkins University, Baltimore, MD 21218, USA

ARTICLE INFO

Article history:

ABSTRACT

A novel amphiphilic and cationic triblock copolymer consisting of monomethoxy poly(ethylene glycol),



Scheme 1. Synthesis pathway of $mPEG_{45}$-*b*-PCL_{100}-*b*-$PPEEA_{12}$ and schematic drawing of self-assembled cationic micellar nanoparticles and loading of siRNA.

Biomaterials 29 (2008) 4348–4355

Macromolecular Bioscience

Macromolecular Journals

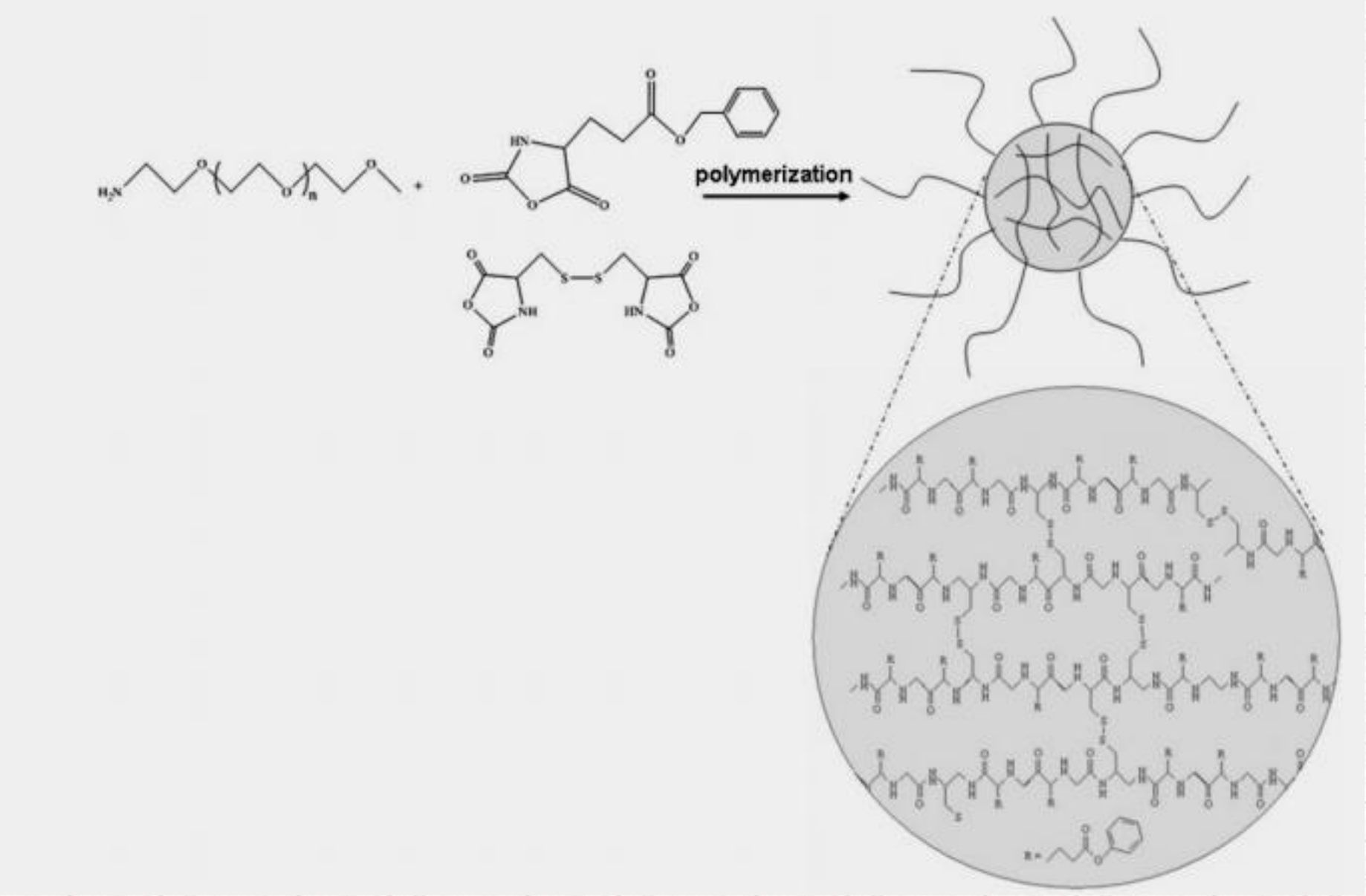
Full Paper

Disulfide Core Cross-Linked PEGylated Polypeptide Nanogel Prepared by a One-Step Ring Opening Copolymerization of *N*-Carboxyanhydrides for Drug Delivery

Tao Xing, Bin Lai, Xiaodong Ye, Lifeng Yan*

Macromol. Biosci. 2011, 11, 962–969

二、生物材料 • 聚多肽体系

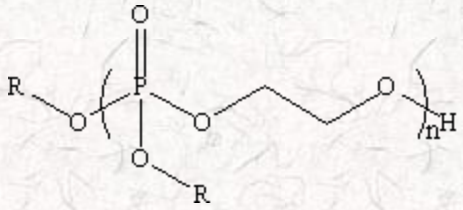


Macromol. Biosci. 2011, 11, 962–969

二、生物材料 • 聚多肽体系

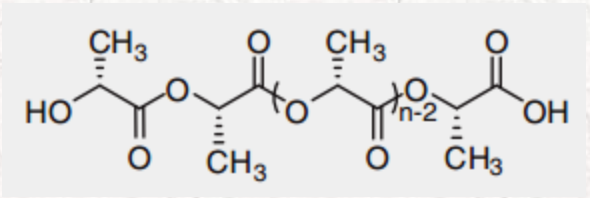
常用生物材料

亲水性链段



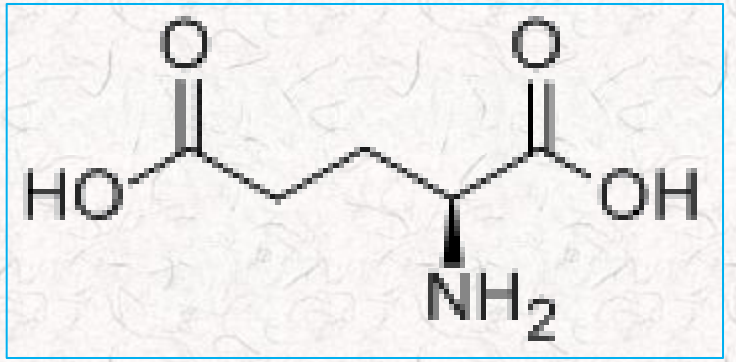
聚乙烯醇等

疏水链段

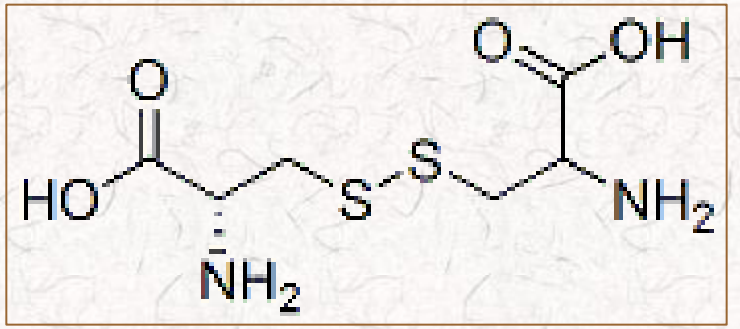


聚多肽等

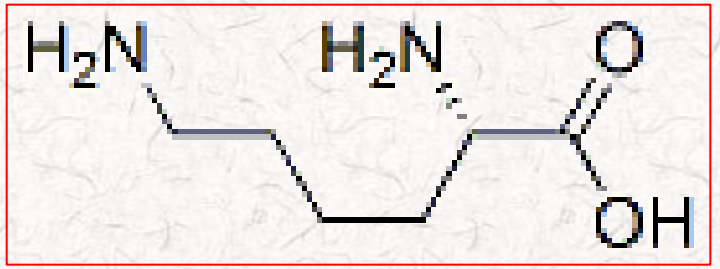
谷氨酸



胱氨酸

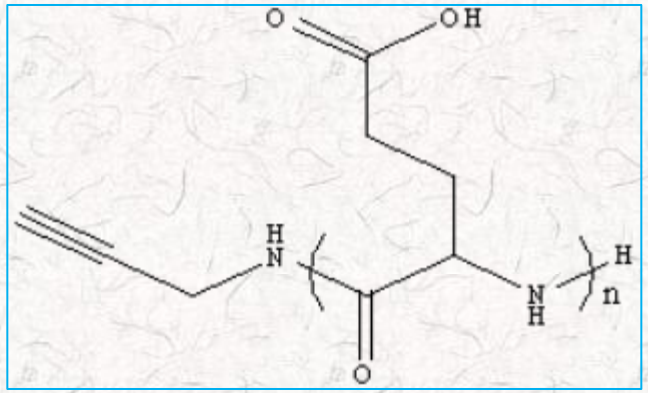


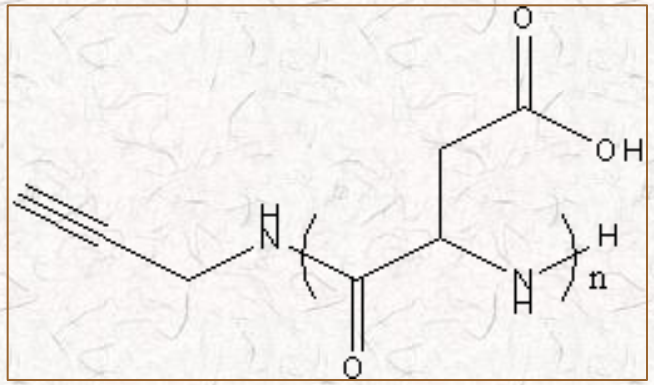
赖氨酸



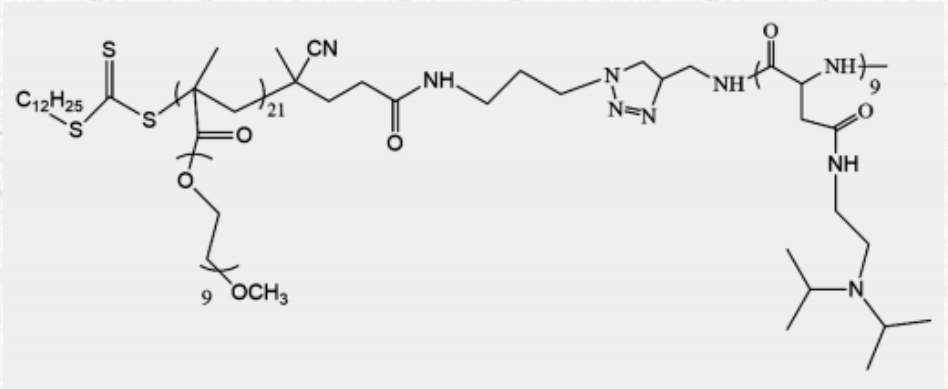
二、生物材料 • 聚多肽体系

目前实验室可以做的多肽类型

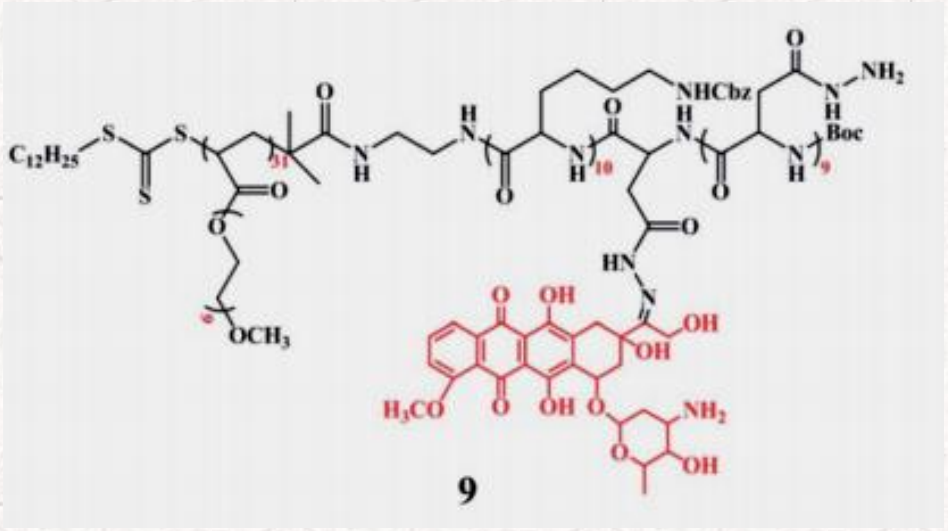




谷氨酸/天冬氨酸多肽



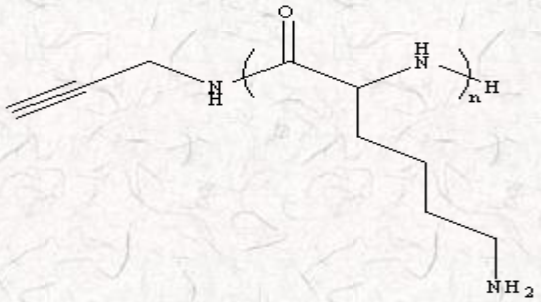
ACS Appl. Mater. Interfaces 2016, 8, 8980–8990



RSC Adv., 2014, 4, 28186–28194

二、生物材料 • 聚多肽体系

目前实验室可以做的多肽类型



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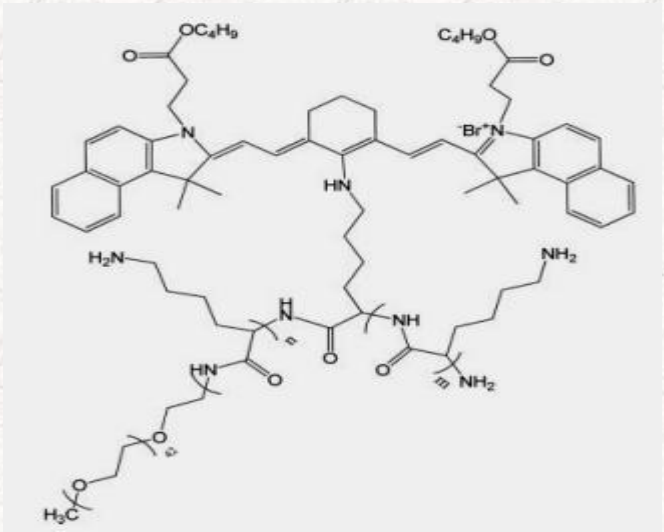
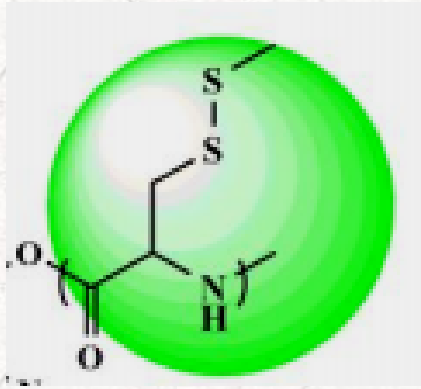
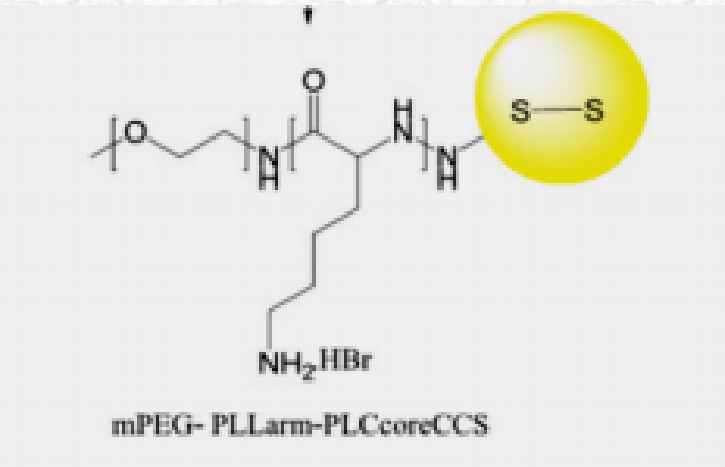


Journal of Macromolecular Science, Part A:
Pure and Applied Chemistry (2013) 50, 90–98



胱氨酸多肽



Polym. Chem., 2016, 7, 951–957

ACS APPLIED MATERIALS & INTERFACES

Research Article

www.acsami.org

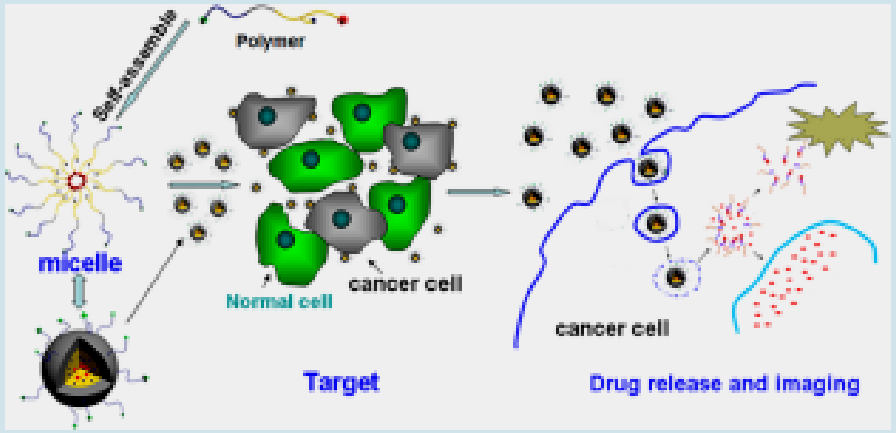
Galactose Targeted pH-Responsive Copolymer Conjugated with Near Infrared Fluorescence Probe for Imaging of Intelligent Drug Delivery

Liyi Fu,[†] Chunyang Sun,[‡] and Lifeng Yan*[,†]

[†]CAS Key Laboratory of Soft Matter Chemistry, Hefei National Laboratory for Physical Sciences at the Microscale, Collaborative Innovation Center of Chemistry for Energy Materials, and Department of Chemical Physics and [‡]School of Life Sciences, University of Science and Technology of China, Hefei, 230026, P.R. China

Supporting Information

ABSTRACT: Theranostic polymeric nanomaterials are of special important in cancer treatment. Here, novel galactose targeted pH-responsive amphiphilic multiblock copolymer conjugated with both drug and near-infrared fluorescence (NIR) probe has been designed and prepared by a four-steps process: (1) ring-opening polymerization (ROP) of *N*-carboxy anhydride (NCA) monomers using propargylamine as initiator; (2) reversible addition−fragmentation chain transfer (RAFT) polymerization of oligo(ethylene glycol) methacrylate (OEGMA) and gal monomer by an azido modified RAFT agent; (3) combing the obtained two polymeric segments by



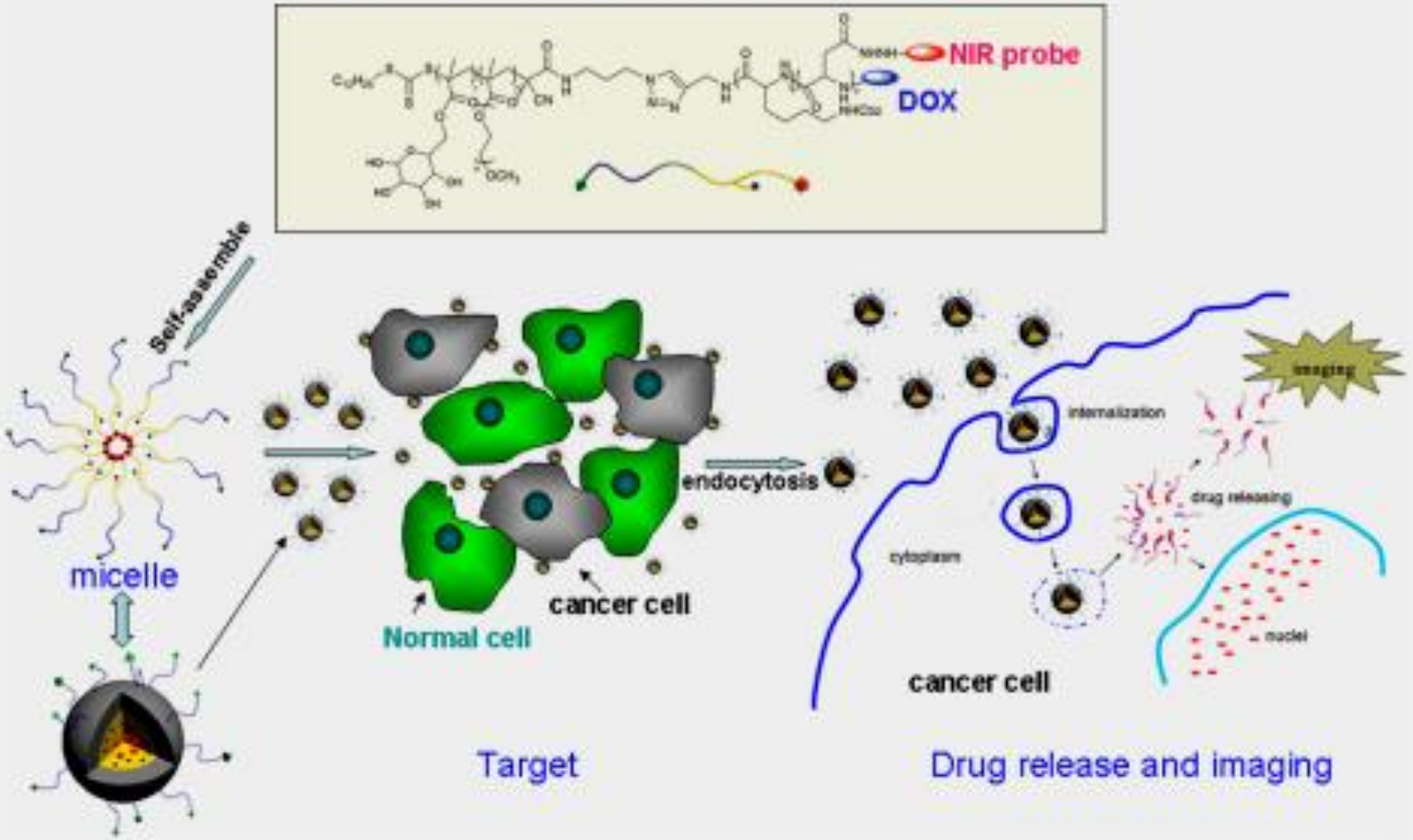
ACS Appl. Mater. Interfaces 2015, 7, 2104−2115

二、生物材料 • 近红外荧光成像

ACS Applied Materials & Interfaces

Research Article

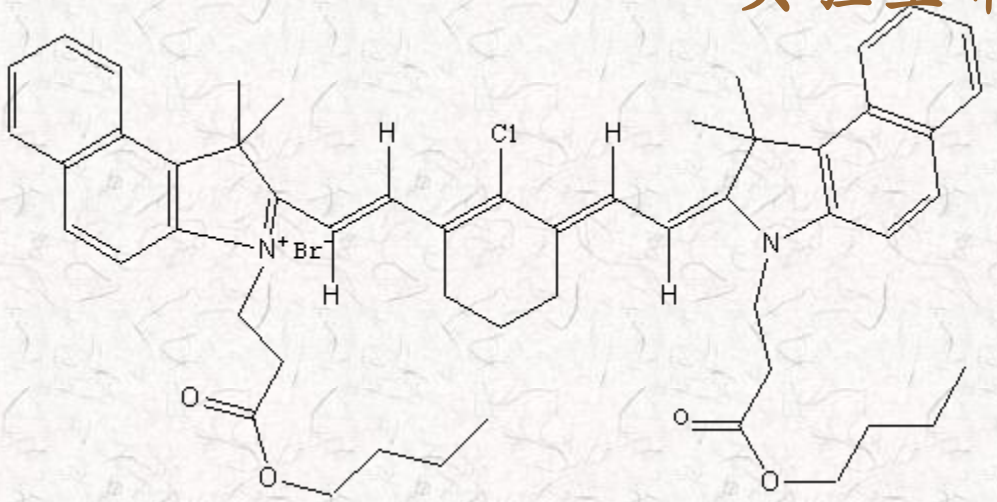
Scheme 1. Structure of Ligand Targeted Copolymer Conjugated with DOX and NIR Probe, Micellization, Selective Accumulation in Liver Cancer Cell, and Imaging of the Endocytosis of the Micelle with Subsequent pH Triggered Drug Release

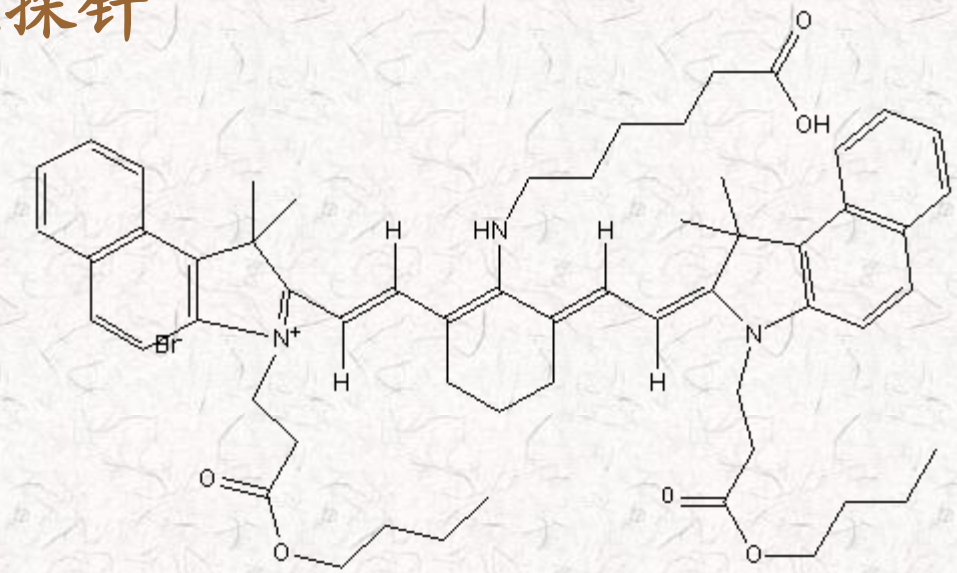


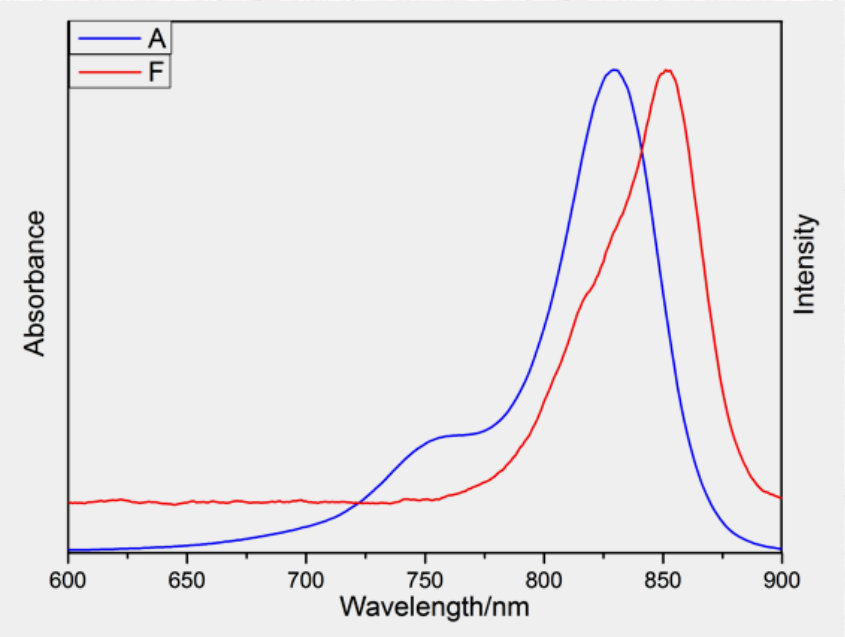
ACS Appl. Mater. Interfaces 2015, 7, 2104−2115

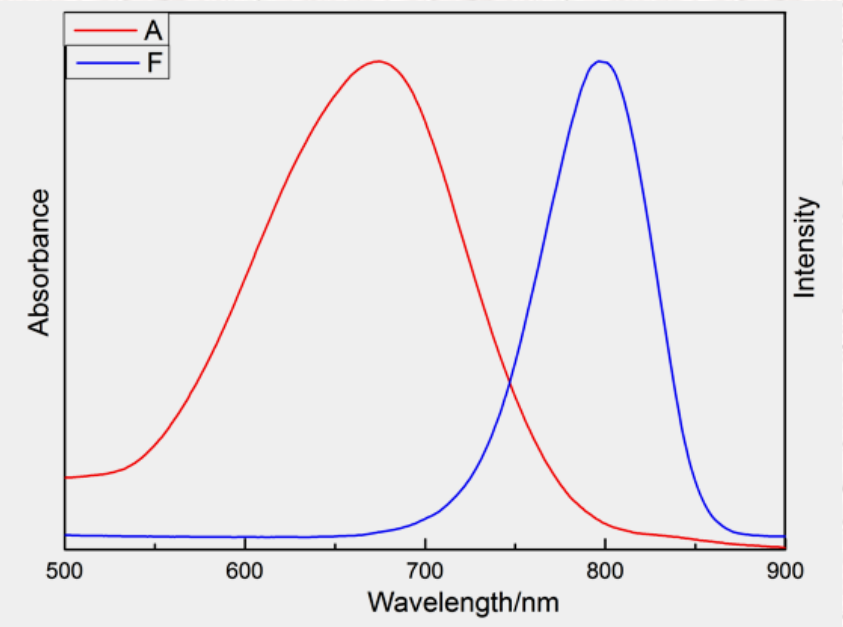
二、生物材料 • 近红外荧光成像

实验室常用的荧光探针



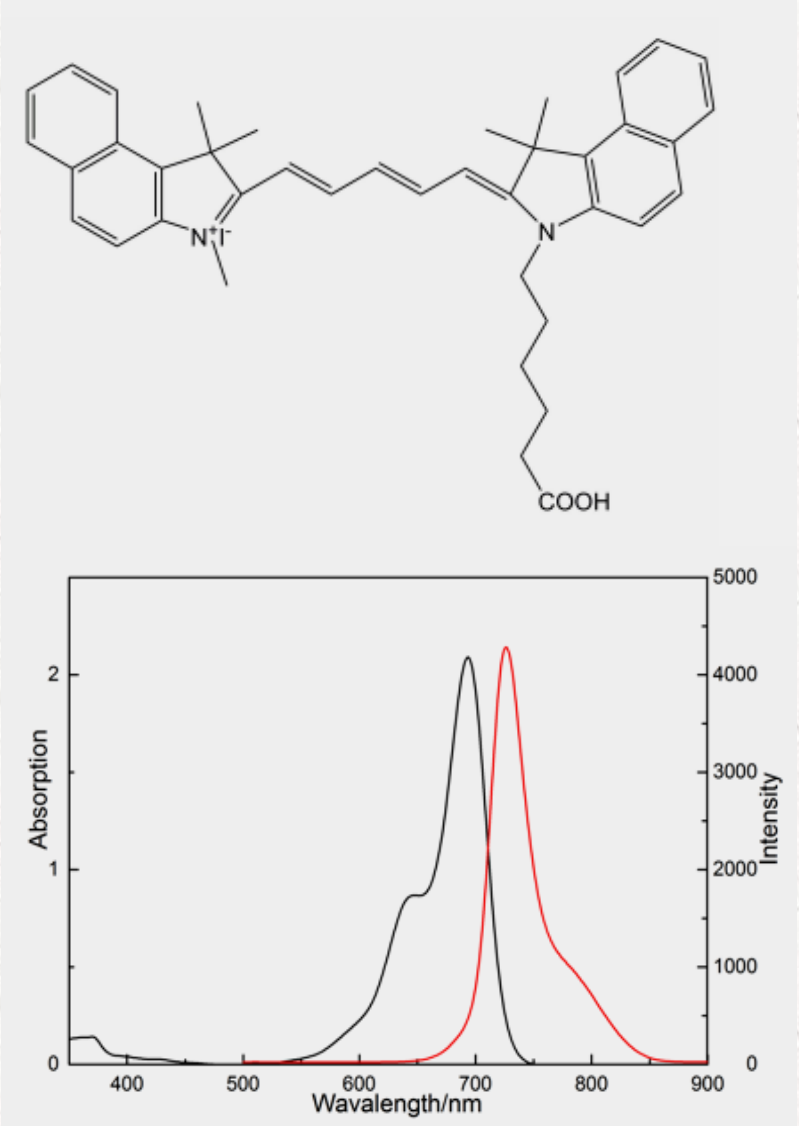


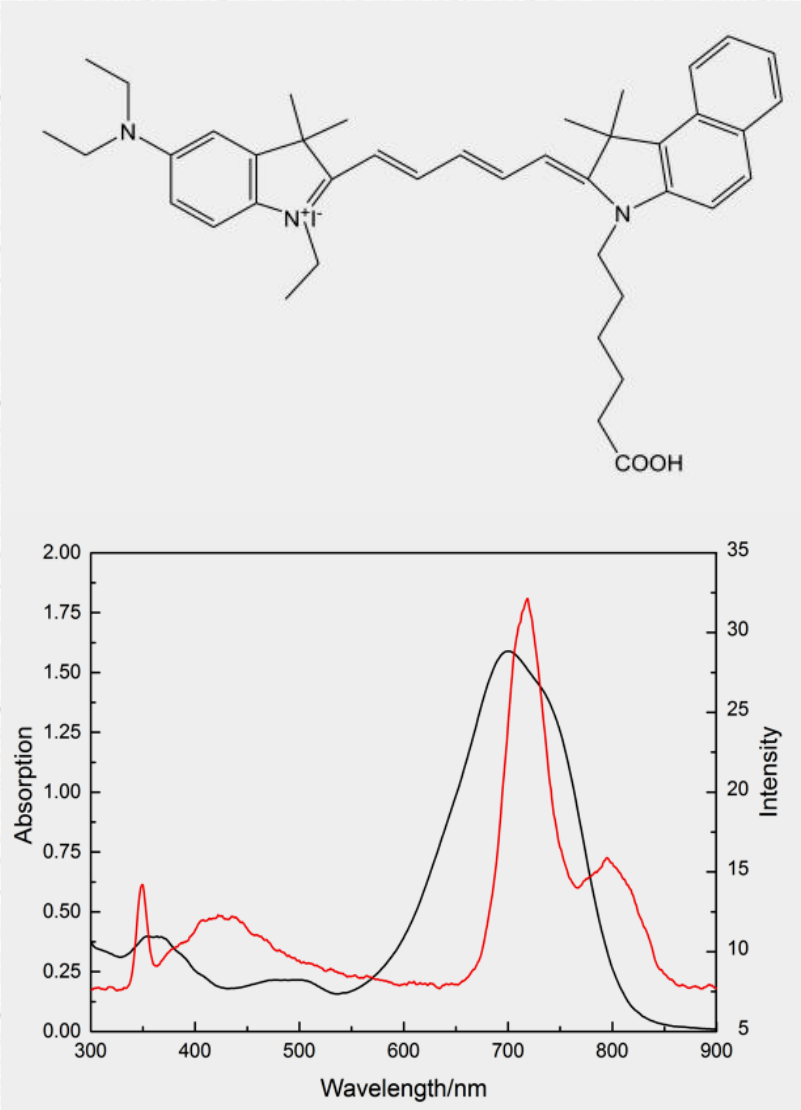




二、生物材料 • 近红外荧光成像

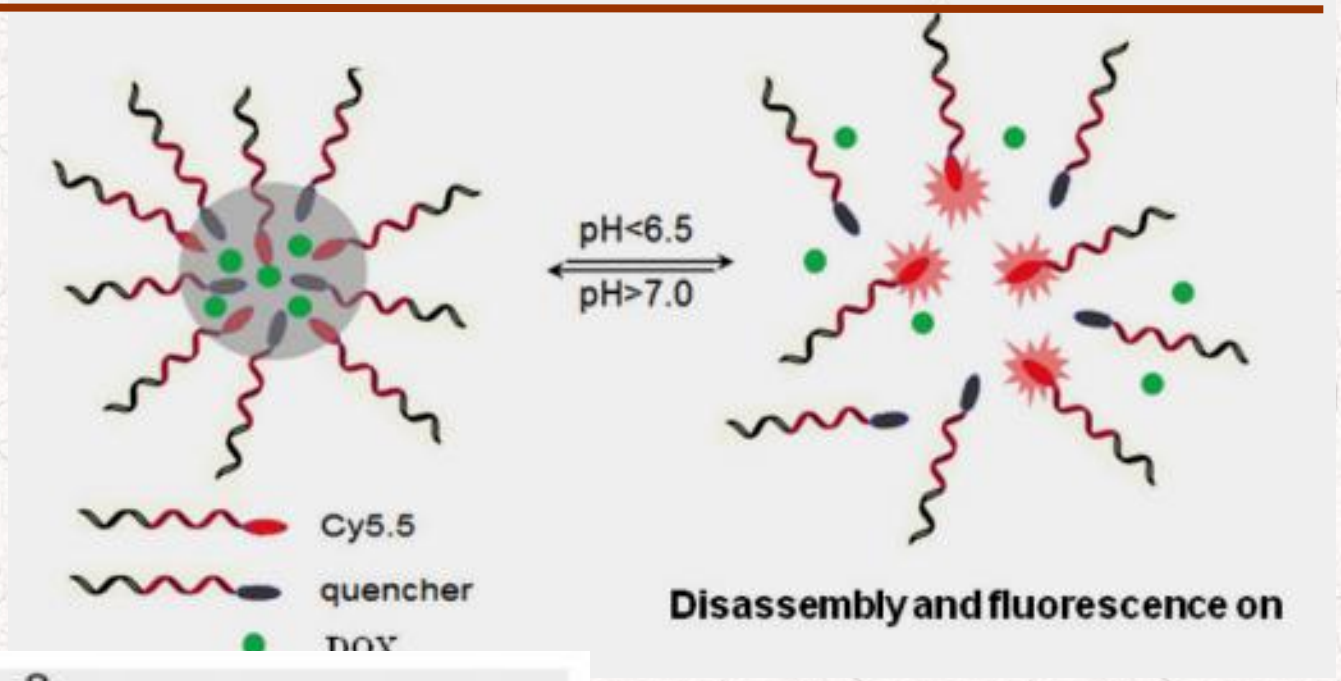
实验室常用的荧光探针



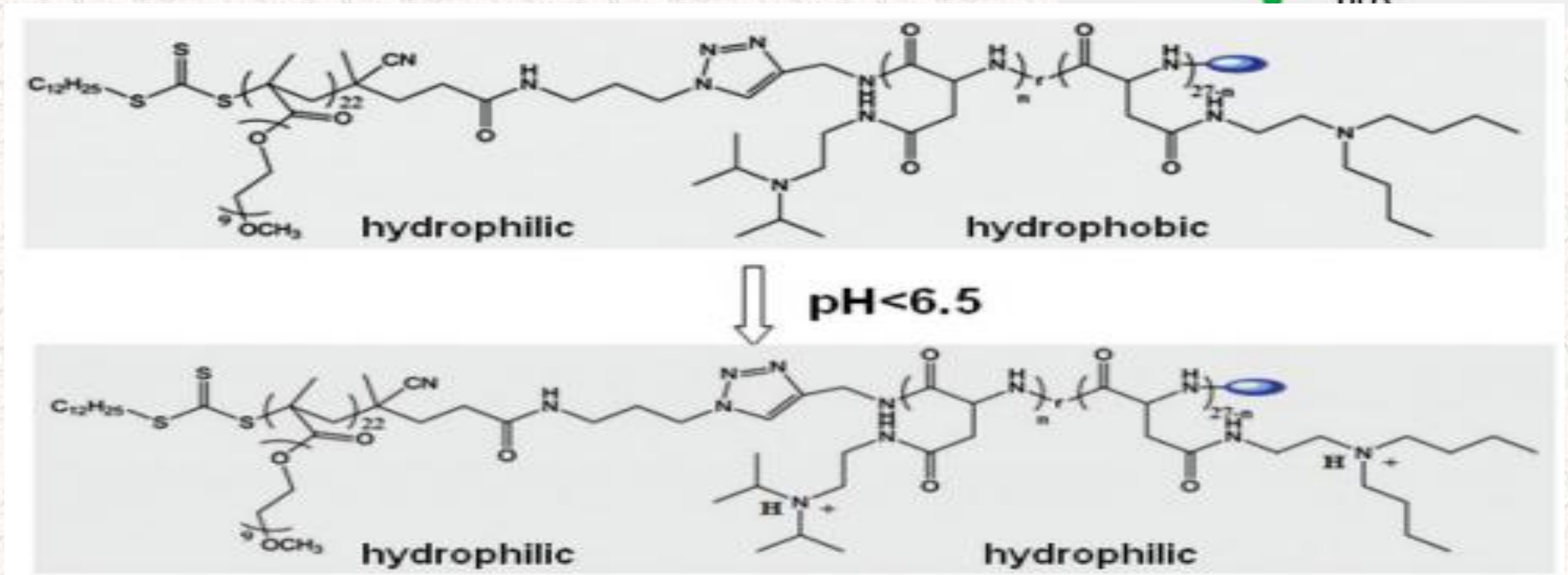


二、生物材料 • 近红外荧光成像

pH响应的off-on载药体系



Polym. Chem., 2017, 8, 1028-1038



ACS APPLIED MATERIALS & INTERFACES

Research Article

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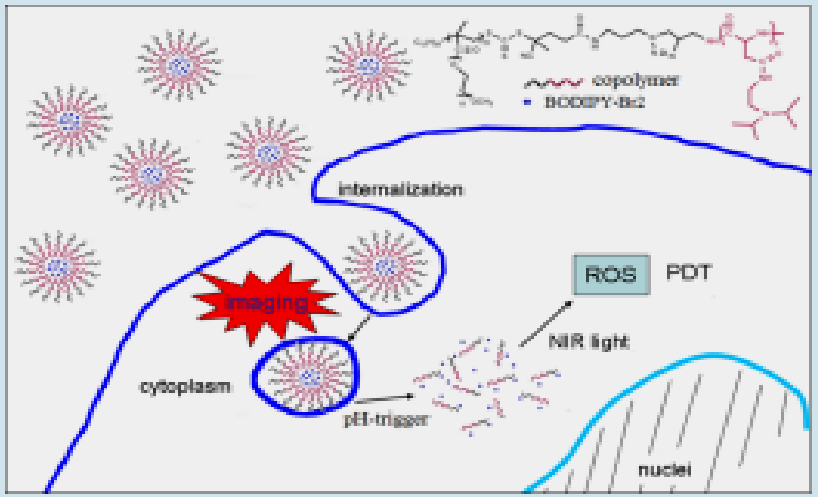
pH-Triggered Polypeptides Nanoparticles for Efficient BODIPY Imaging-Guided Near Infrared Photodynamic Therapy

Le Liu, Liyi Fu, Titao Jing, Zheng Ruan, and Lifeng Yan*

CAS Key Laboratory of Soft Matter Chemistry, National Synchrotron Radiation Laboratory, iChEM, and Department of Chemical Physics, University of Science and Technology of China, Hefei 230026, P. R. China

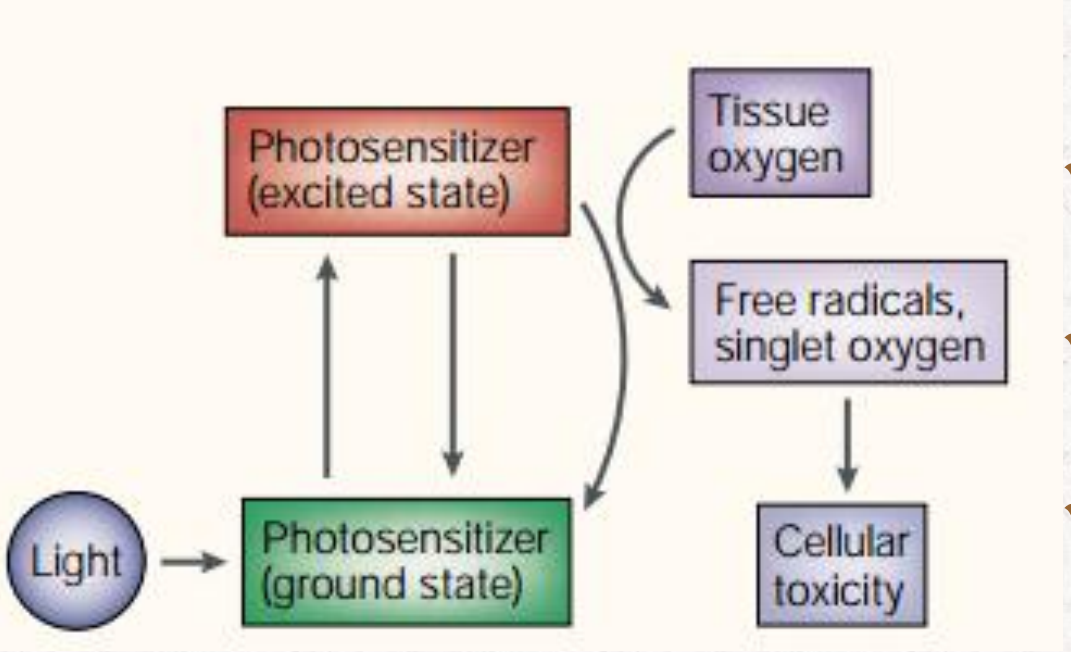
Supporting Information

ABSTRACT: An efficient pH-responsive multifunctional polypeptide micelle for simultaneous imaging and in vitro photodynamic therapy (PDT) has been prepared. The goal here is to detect and treat cancer cells by near-infrared fluorescence (NIRF) imaging and PDT synchronously. A photosensitizer BODIPY-Br_2 with efficient singlet oxygen generation was synthesized at first which owns both seductive abilities in fluorescence emission and reactive oxygen species (ROS) generation under light irradiation. Then, amphiphilic copolymer micelles pH-triggered dis-assembly were synthesized from *N*-carboxyanhydride (NCA) monomer via a ring-opening polymerization and click reaction for the loading of BODIPY-Br_2 by hydrophobic interaction, and the driving force is the protonation of the diisopropylethylamine groups conjugated to the

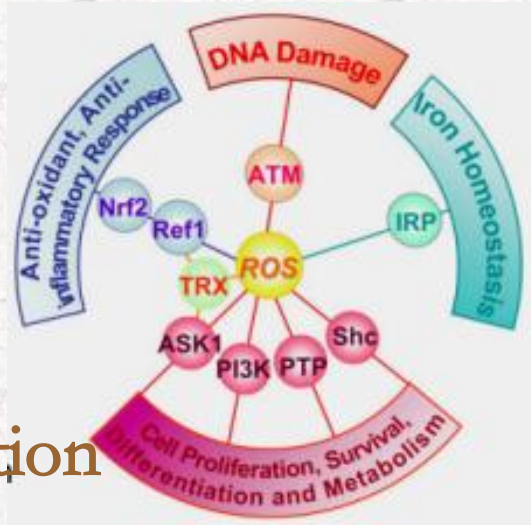


ACS Appl. Mater. Interfaces 2016, 8, 8980−8990

光动力诊疗（PDT）机理



- ✓ direct killing of tumour cells
- ✓ death of tumour tissue
- ✓ local and systemic inflammation



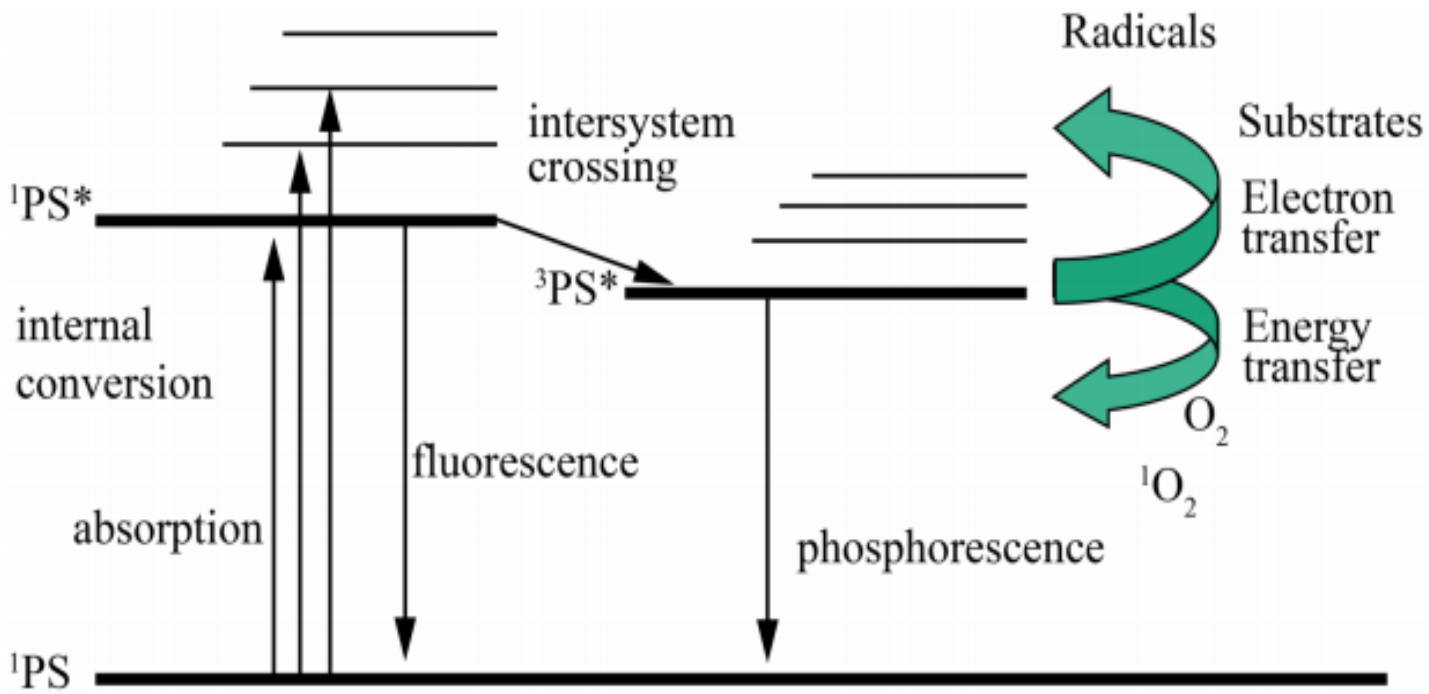
Nature Reviews Cancer 3, 380-387 (May 2003)

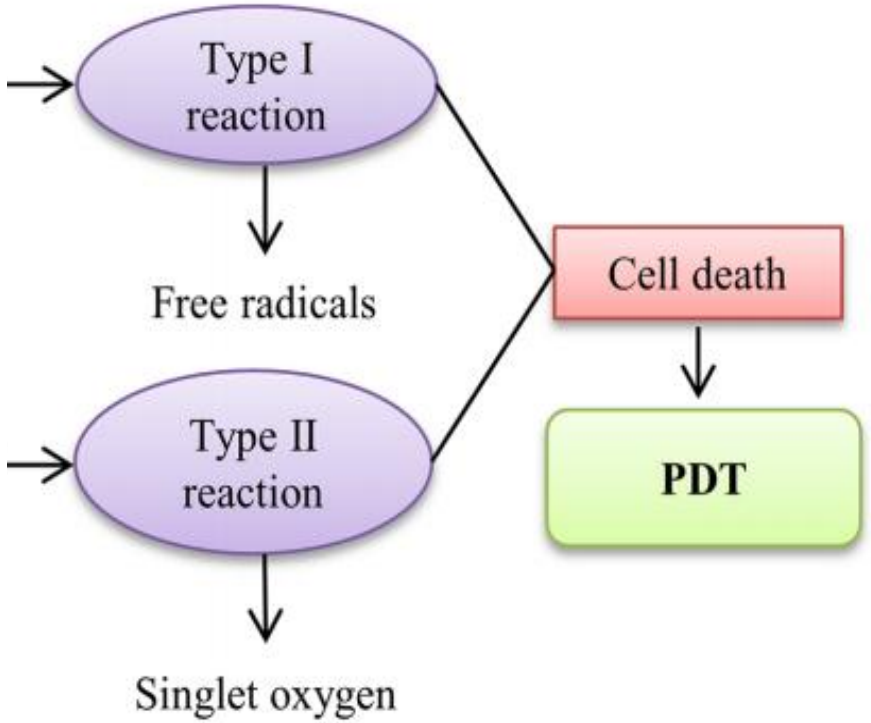
Photochem. Photobiol. Sci., 2015, 14, 1765-1780

Cellular Signalling 24 (2012) 981–990

二、生物材料 • 光动力诊疗（PDT）

活性氧（ROS）产生机理





J. Porphyrins Phthalocyanines 2017; 21: 240–256

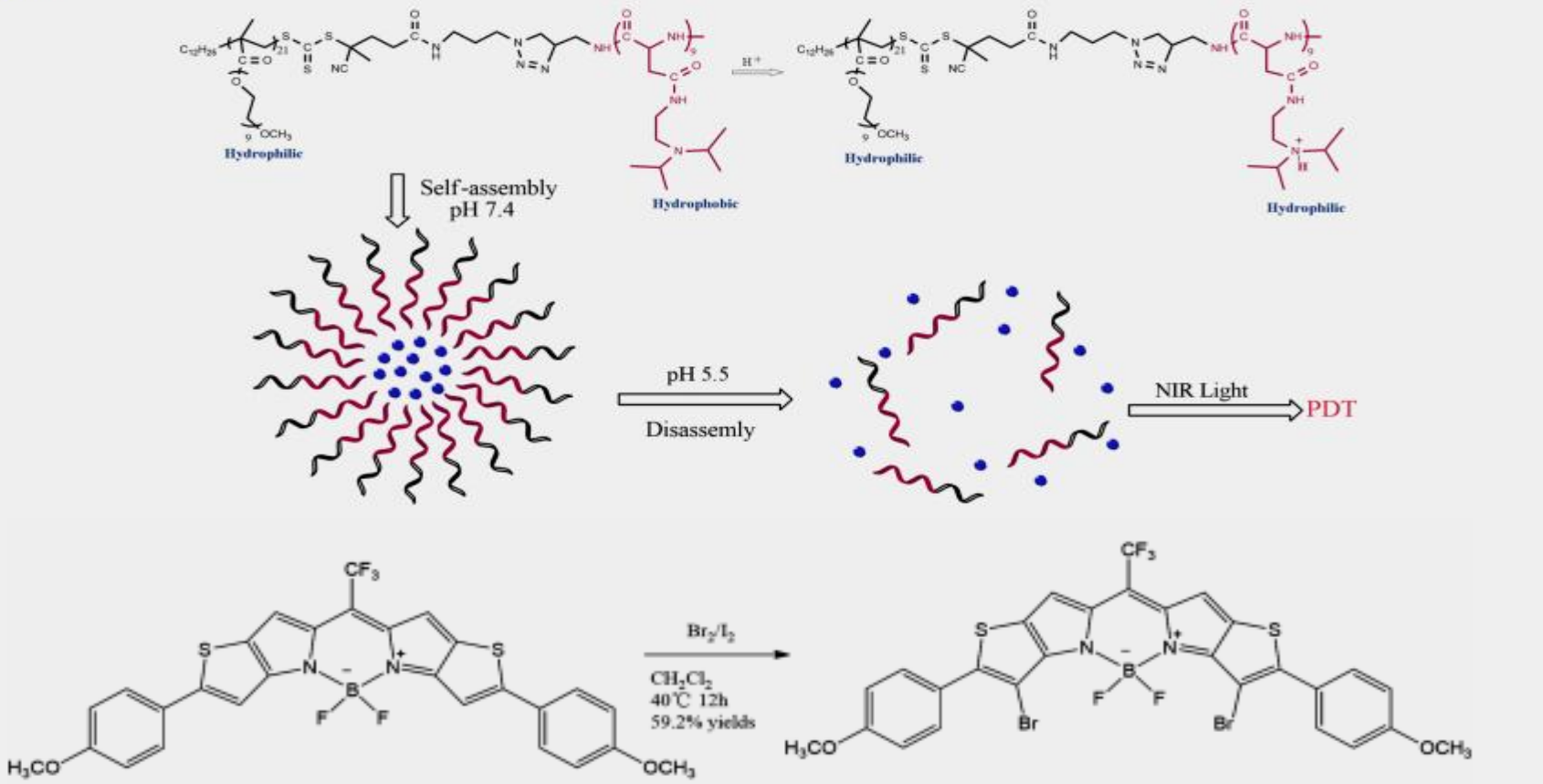
Chem. Rev. 2015, 115, 1990−2042

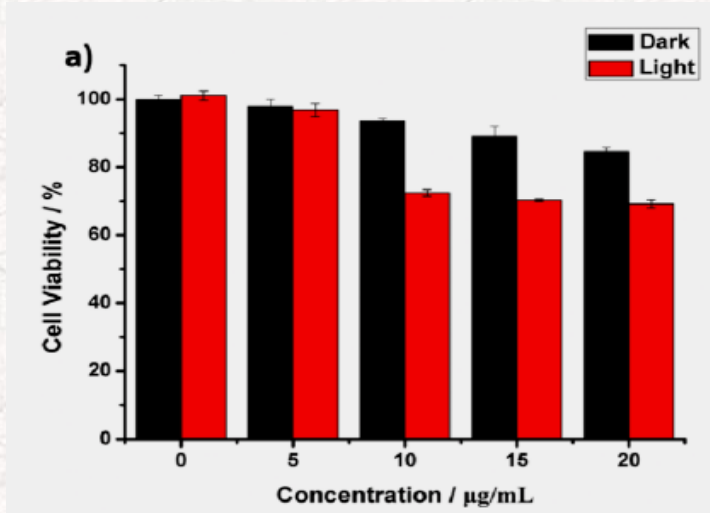
二、生物材料 • 光动力诊疗（PDT）

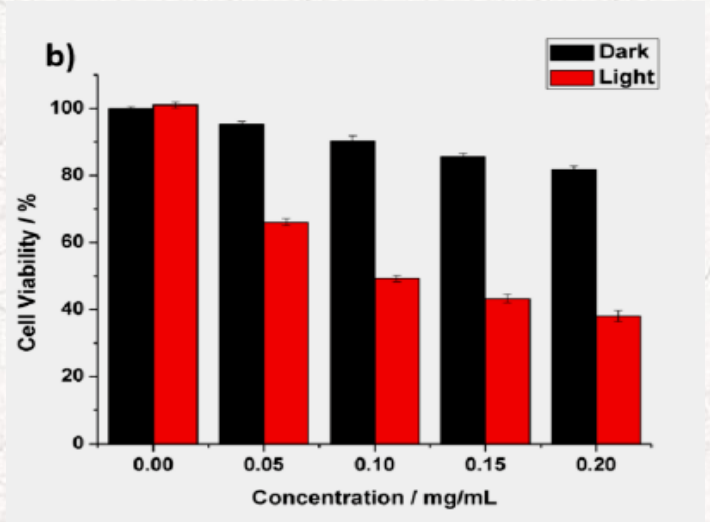
近红外成像指导的光动力诊疗

ACS Applied Materials & Interfaces　Research Article

Scheme 1. Structure of Polypeptides Loading BODIPY-Br_2, Micellization, and pH Triggered Drug Release Followed by NIR PDT



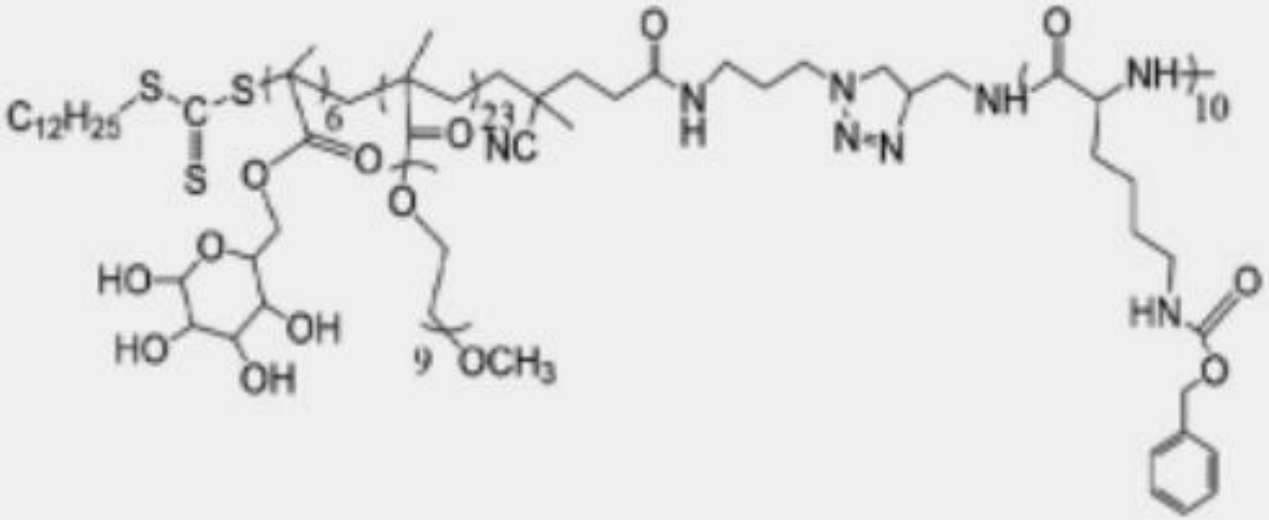


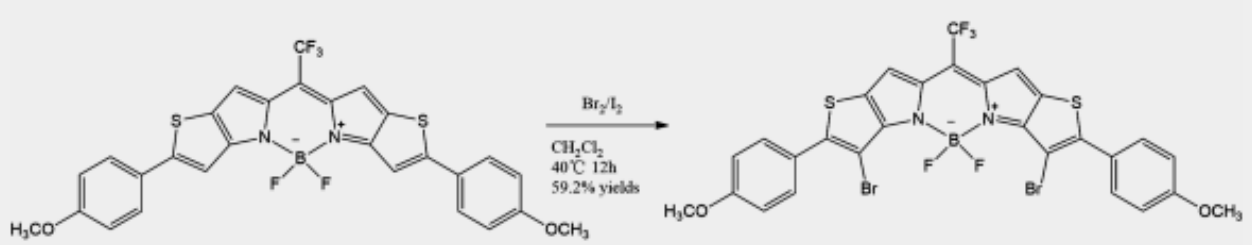


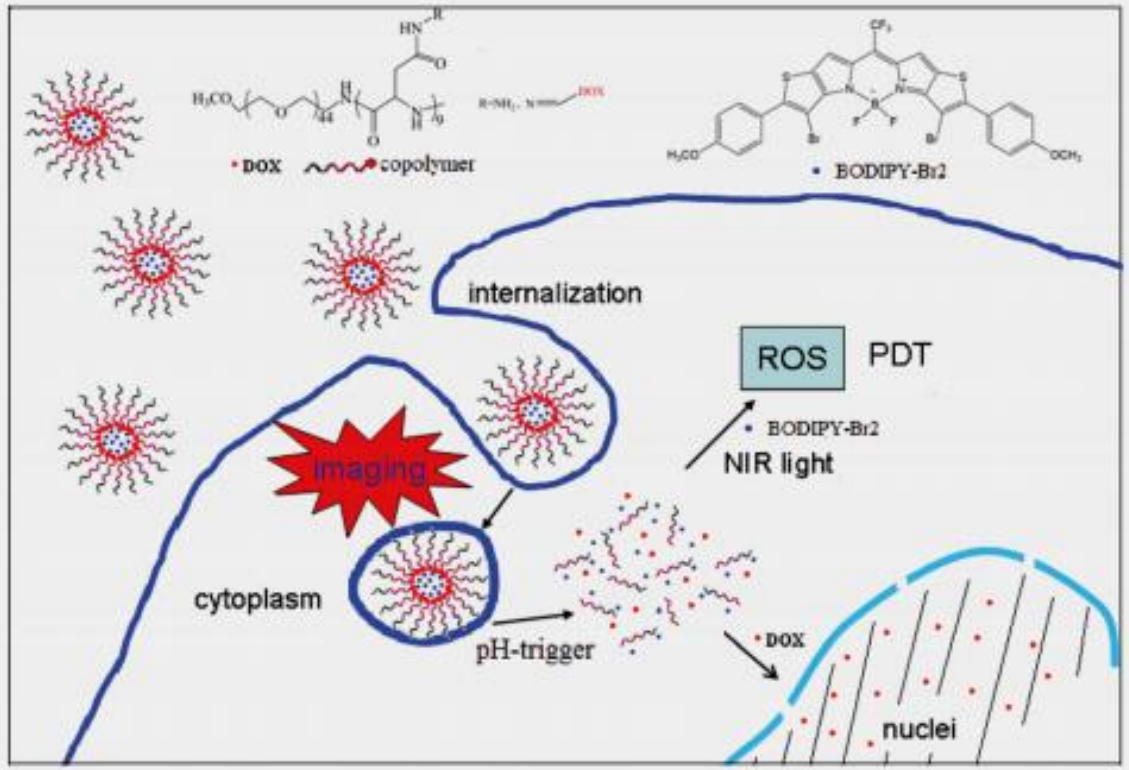
ACS Appl. Mater. Interfaces 2016, 8, 8980–8990

二、生物材料 • 光动力诊疗（PDT）

靶向+光动力诊疗



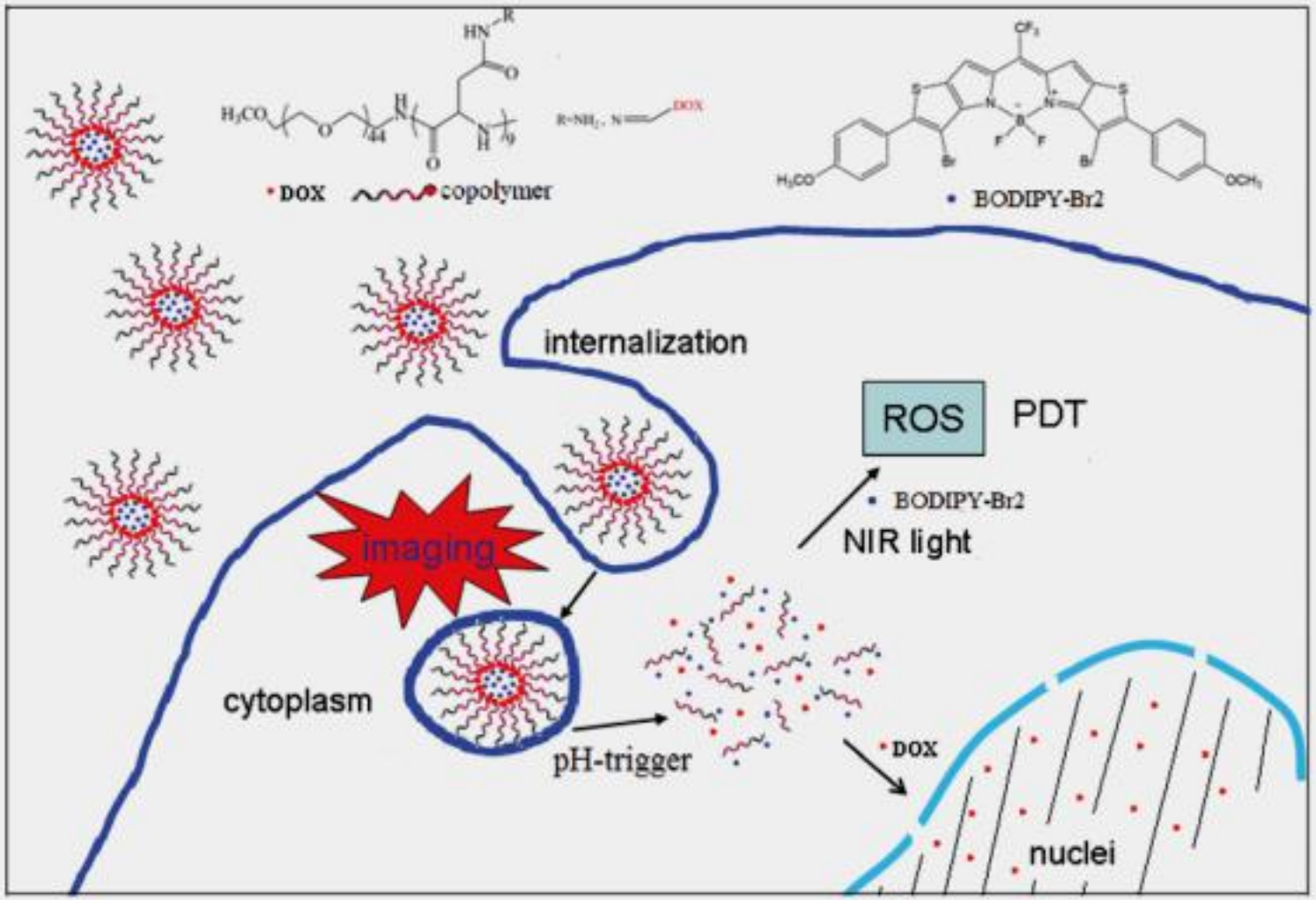




Scheme 1 Self-assembly of micelles of the BODIPY and DOX containing micelles and demicellization under an acidic environment in a cell.

Biomater. Sci., 2016, 4,1638

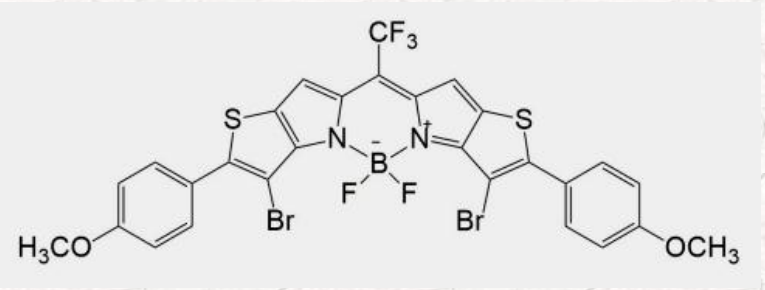
化疗与光动力的组合疗法

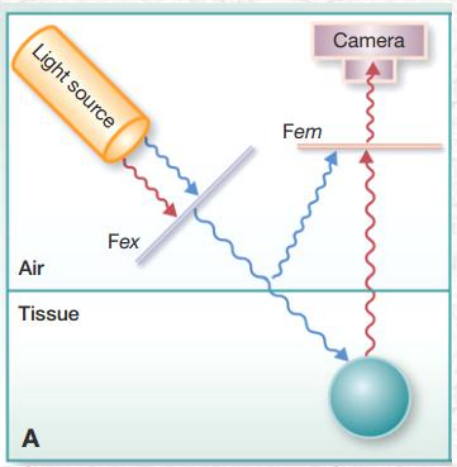


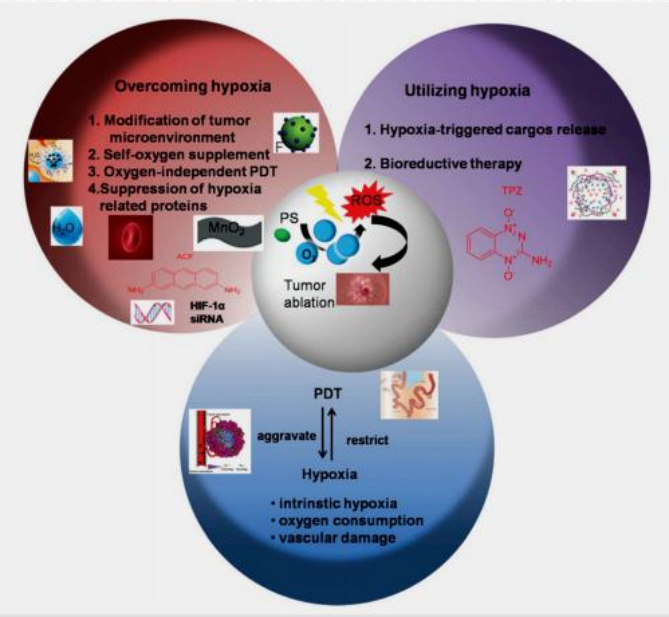
Biomater. Sci., 2017, 5, 313-321

二、生物材料 • 光动力诊疗（PDT）

光动力诊疗的瓶颈







- ✓ 溶解性
- ✓ 可反应官能团
- ✓ 单线态氧量子产率
- ✓ 稳定性

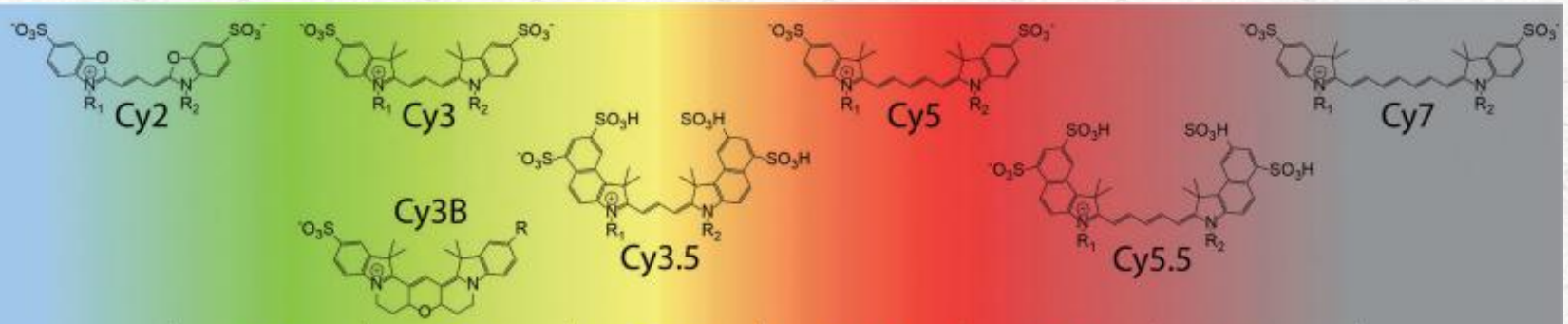
- ✓ 光源强度
- ✓ PDT设备

肿瘤组织乏氧问题

二、生物材料 • 自修复荧光探针

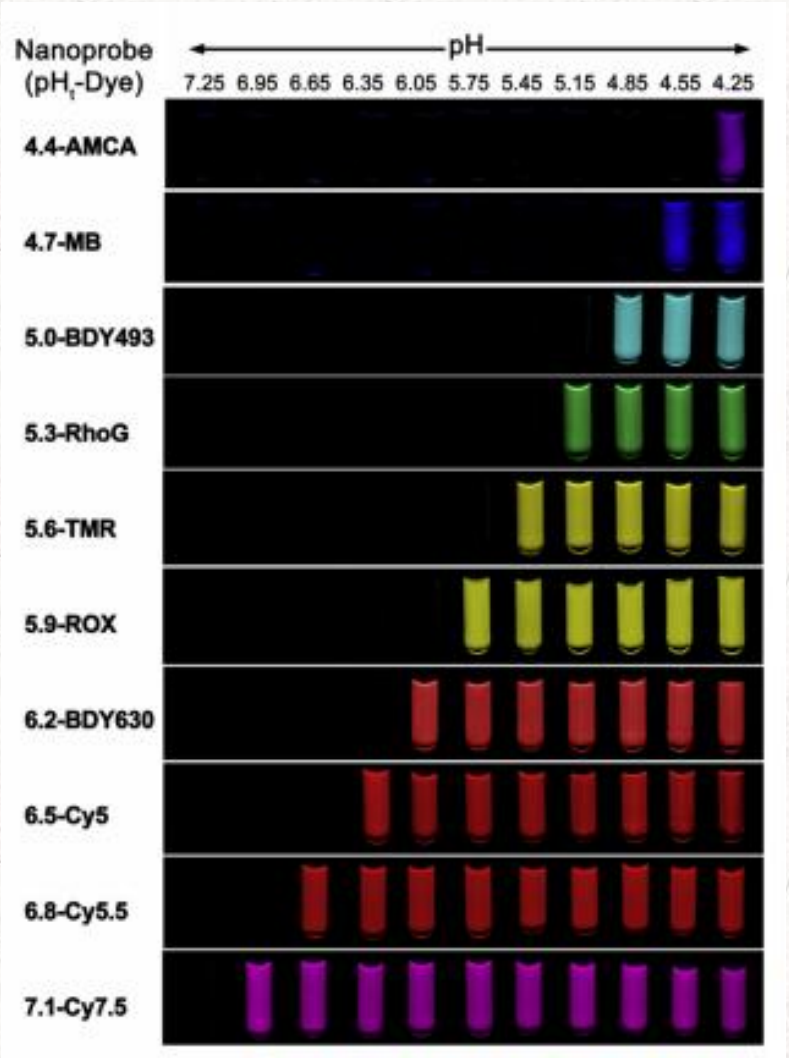
常见Cy荧光探针

b



	Cy2	Cy3	Cy3B	Cy3.5	Cy5	Cy5.5	Cy7
λ_{abs} (nm)	489 nm [i,a]	550 nm [i,a]	559 nm [i,a]	581 [i,a]	649 nm [i,a]	675 nm [i,a]	747 nm [i,a]
λ_F (nm)	506 nm [i,a]	570 nm [i,a]	570 nm [i,a]	596 [i,a]	670 nm [i,a]	694 nm [i,a]	776 nm [i,a]
ε_{max} (10^5 $M^{-1}cm^{-1}$)	1.3 [ii,b,*]	1.5 [iii,a] 1.5 [v,a/b]	1.3 [iii,a]	1.2 [xiv,a] 1.25 [xiv,c]	2.2 [iv,b,*] 2.5 [v,a/b]	1.9 [xiv,a] 1.95 [xiv,c]	2.5 [vi,b,*] 2.0 [v,a/b]
τ_F (ns)	0.2 [vii,a]	0.2 [vii,a] < 0.3 [iii,a] 0.18 [xiii,a]	2.8 [iii,a] 2.7 [xiii,a]	0.6 [xvi,a]	0.9 [vii,a] 0.98 [iv,b,*]	0.83 [xvii,a]	0.4 [vii,a]
Φ_F	0.05 [viii,b,*] 0.04 [xi,e,*] 0.053 [xii,c,*]	0.04 [iii,a] 0.09 [xiii,a] 0.04 [v,a] 0.09[v,b]	0.67 [iii,a] 0.85 [xiii,a]	0.14 [xiv,a] 0.28 [xiv,c]	0.21 [iv,b,*] 0.27 [v,a] 0.4 [v,b]	0.23 [xiv,a] 0.24 [xiv,c]	0.28 [vi,b,*]
τ_T (μs)	[–]	520 [xv,b,*] 3.9 [ix,c]	[–]	[–]	60 [iv,b,*] 63 [x,d]	[–]	[–]
Φ_{ISC}	< 0.001 [xi,e,*]	< 0.001 [iv,e,*] 0.03 [ix,c]	[–]	[–]	< 0.003 [iv,b,*]	[–]	[–]

Chem. Soc. Rev., 2014,43, 1044



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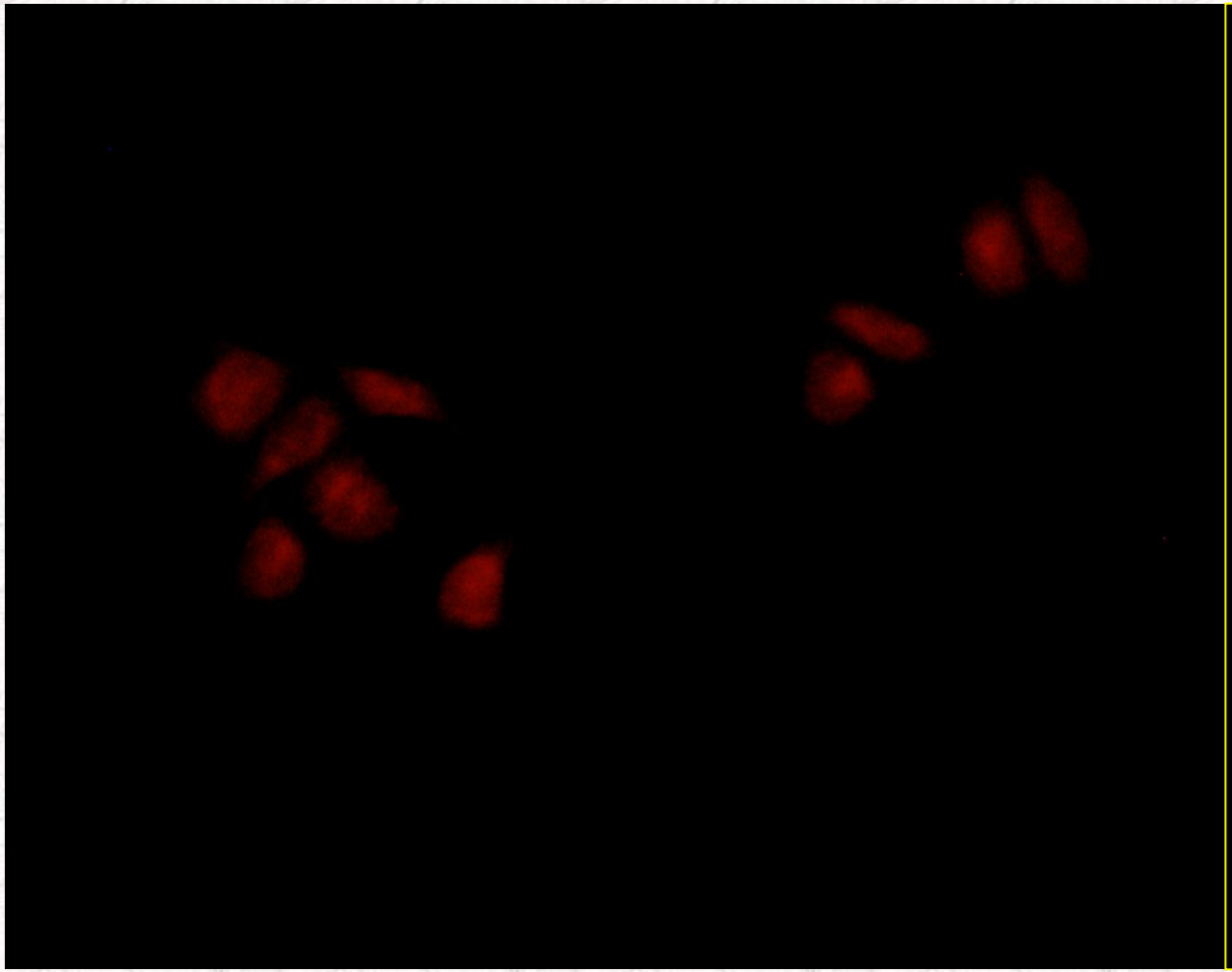
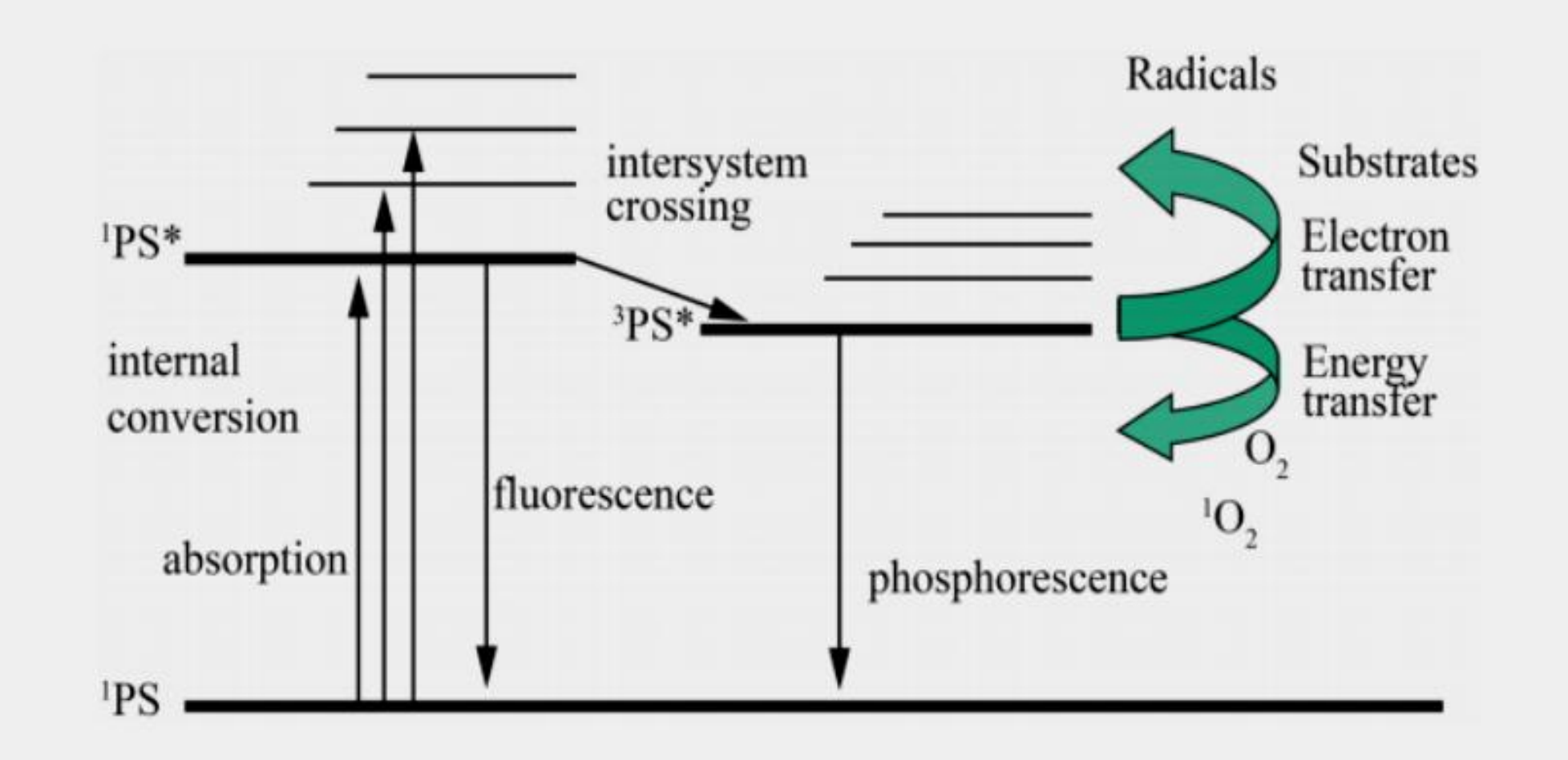
二、生物材料 • 自修复荧光探针

实际成像过程中荧光探针的漂白

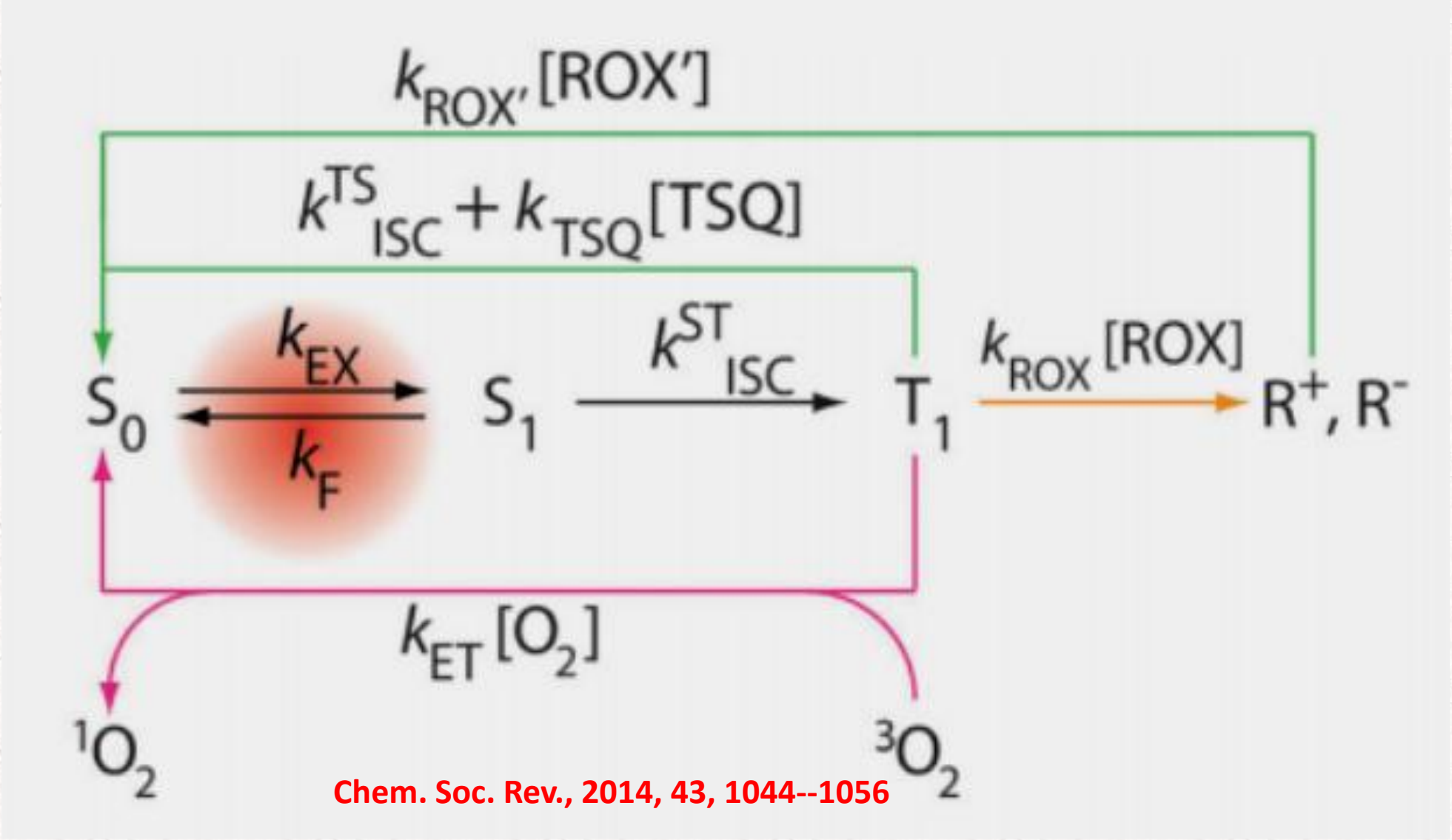


荧光漂白原理



J. Porphyrins Phthalocyanines 2017; 21: 240–256

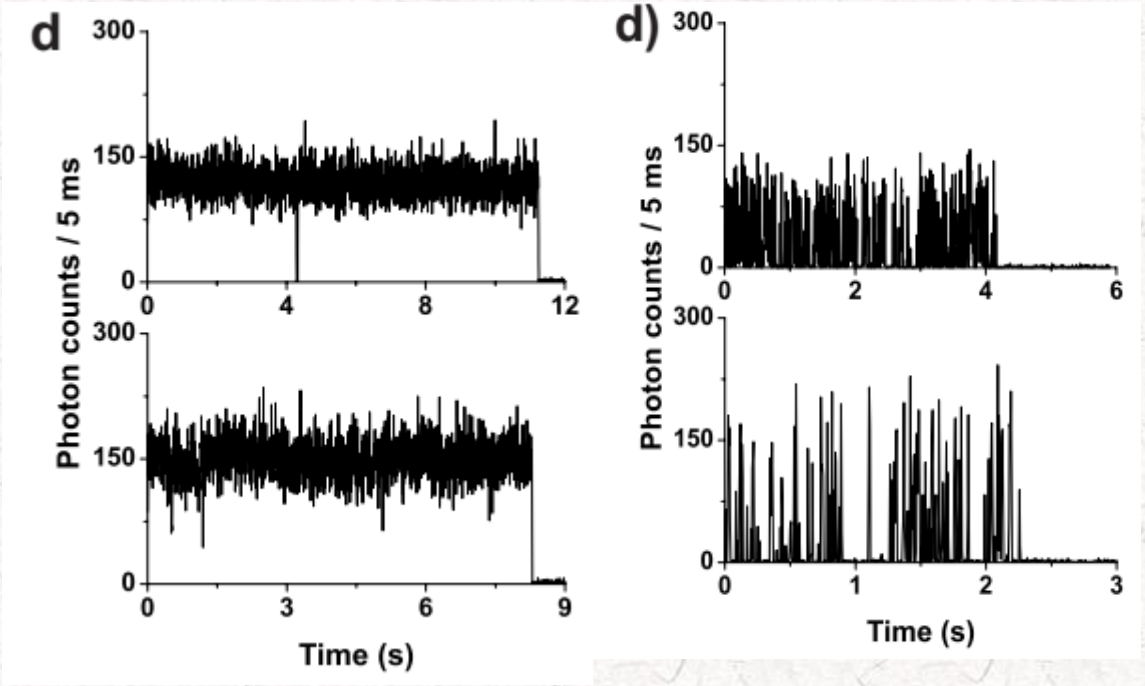
荧光漂白路径



Chem. Soc. Rev., 2014, 43, 1044--1056

二、生物材料 • 自修复荧光探针

荧光闪烁与荧光漂白的理论与测试现实



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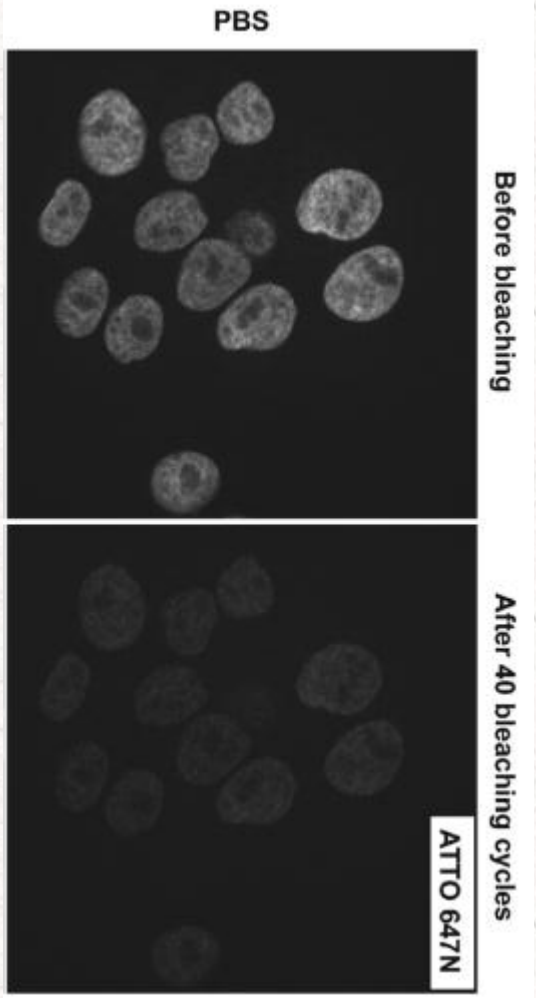
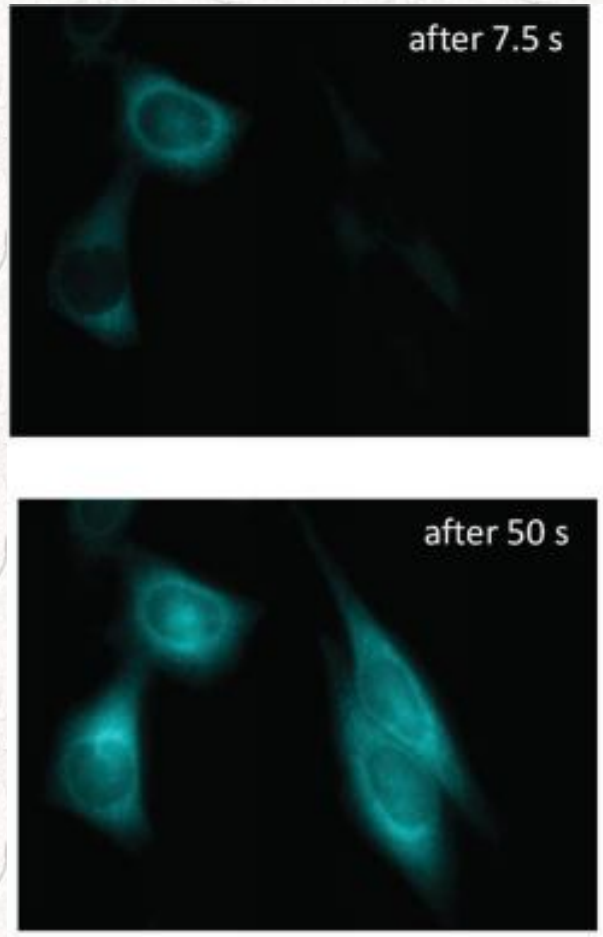


Phys. Chem. Chem. Phys., 2011, 13, 6699–6709



Integr. Biol., 2016, 8, 177--193

三、过来人的心里话

1、避免成为实验室的小白鼠

✓ 实验室要发展，需要有学生做新课题新方向的前期调研

✓ 要有一部分学生去做拓展实验室现有研究的方向

——导师视角

✓ 要毕业，要有好的发展，一定要有成果

✓ 只有苦劳，却很难有功劳，替别人做嫁衣

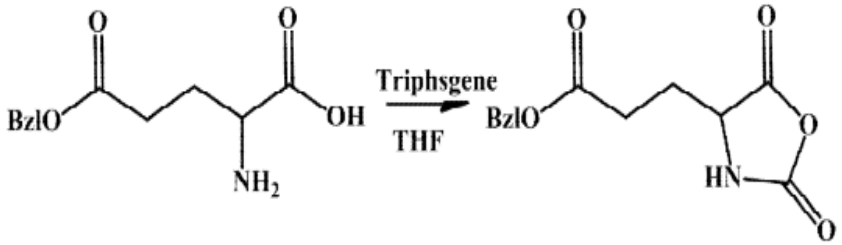
——学生视角

2、努力抱大腿

三、过来人的心里话

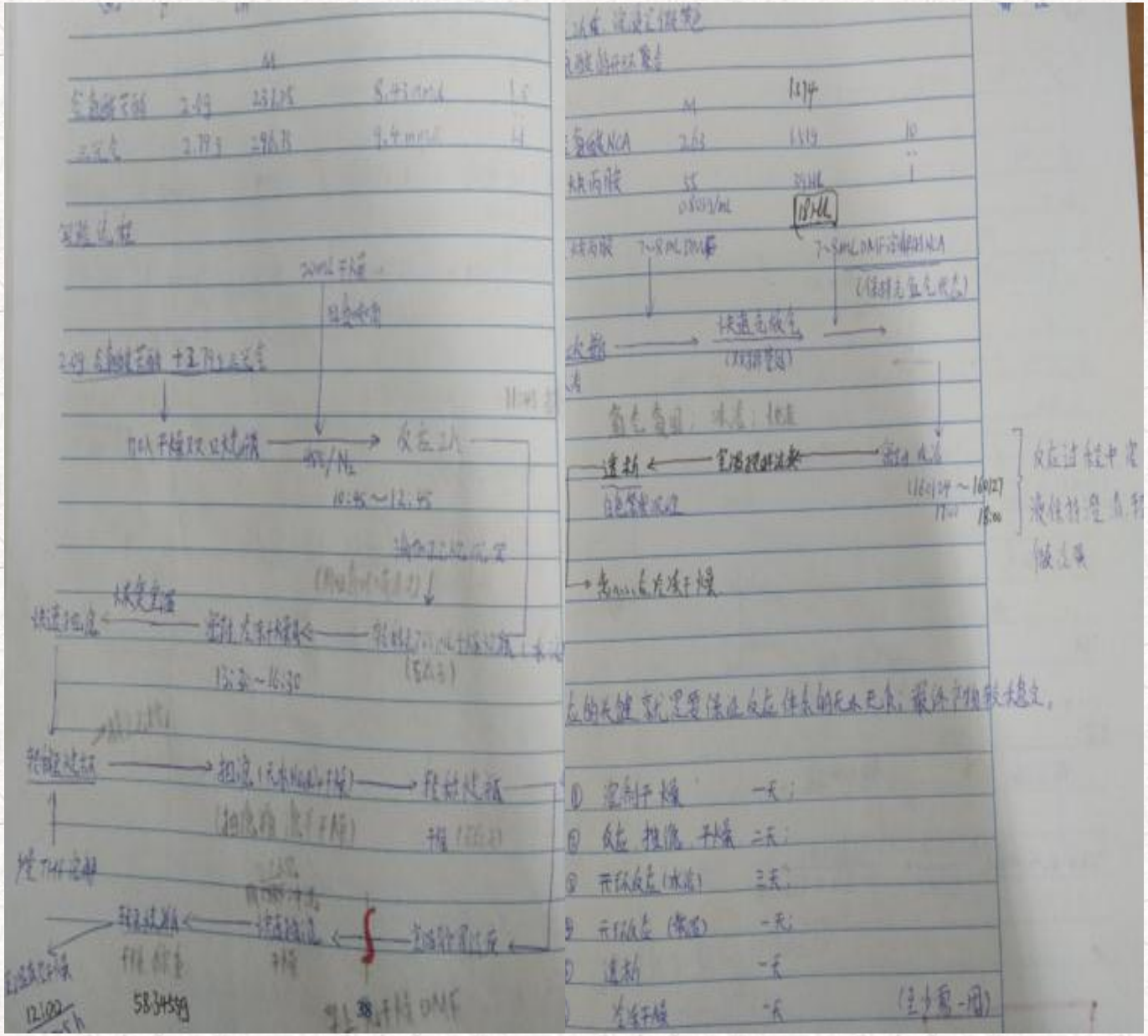
2.2.4 谷氨酸 NCA（Glu-NCA）的合成

将 2.0 g 苄基保护的谷氨酸悬浮于 20 mL 干燥的四氢呋喃中，向此溶液中加入 10 mL 三氯甲基碳酸酯的四氢呋喃溶液，所得的混合物在氮气氛围下于 45 ℃搅拌 2 h，反应完毕后将反应清液沉淀入 60 mL 的正己烷中。收集白色沉淀，于正己烷与四氢呋喃的混合溶剂中结晶三次。收集所得白色晶体，在五氧化二磷存在的情况下于室温真空干燥 12 h。



2.2.5 开环聚合反应

在氮气气氛下，将 0.5 g Cys-NCA 以及 0.5 g Glu-NCA 溶于 5 mL 干燥的 DMF 中。将 mPEG-NH_2 溶于另一预先干燥含有 10 mL DMF 的 Schlenk 瓶中，尔后将单体混合液在氮气气氛下加入到引发剂溶液中。加完后对装置进行密封，于冰浴中搅拌三天。然后将反应物加热至 45 ℃，搅拌 48 h。反应中由于生成二氧化碳，体系压力会升高，反应中排气时将体系与真空线相连，以防止空气进入。反应完毕后首先将反应物沉淀入 100 mL 预冷的无水乙醚中。而后重新溶于 DMF 中，对 1 L 超纯水进行透析 48 h。透析液每隔 12 h 更新一次。



3、不要轻言创新

4、能麻烦别人的一定不要自己动手

- ✓ 自己不能做的
- ✓ 自己不会做的
- ✓ 自己不屑做的

5、先把事情做成，再考虑把事情做好

感谢关注