个人综述材料

姓名	于法标	性别	男	出生年月	1980 年 1 月	职称	研究员
最高学历	研究生	毕业时间	2013 年 7 月		毕业学校及专业	大连理工大学/中科院大连化学物理研究所 物理化学	
最高学位	博士	获得时间	2013 年 7 月		授予学校或单位	大连理工大学	
专业	临床检验诊断学				研究领域	临床检验诊断新技术	

教育和工作简历（包括毕业学校、所学专业，工作单位、岗位任职经历）：

2001.09-2006.07：山东师范大学，大学本科，化学专业

2006.09-2009.07：山东师范大学，硕士研究生（免试），分析化学

2010.09-2013.07：大连理工大学/中科院大连化学物理研究所，博士研究生，物理化学

2013.08-2017.09：中科院烟台海岸带研究所，副研究员， 检验检疫

2017.10- 至今： 海南医学院， 研究员， 临床检验诊断

政治思想、任职资历和主要工作业绩：

简介

于法标，男，汉族，博士生导师，1980 年 1 月出生，籍贯山东省菏泽市，博士研究生学历，2013 年 8 月大连理工大学/中科院大连化学物理研究所毕业后在中科院烟台海岸带研究所工作，于 2017 年 10 月入职海南医学院。海南医学院功能材料与分子影像技术创新团队负责人（海南省首批双百团队）海南省百人计划，海南省高层次人才领军人才、海南省"515 人才工程"第二层次人选、海南省委联系服务重点专家后备人选、中科院青年创新促进会会员。

任职资历

申请人依托海南医学院组建功能材料与分子影像技术创新研究团队，获得海南省首批双百人才团队（储备团队），现有正式在编人员 9 人，分别为于法标研究员、邢艳珑副研究员、王锐副研究员、刘恒研究员、程子译副研究员、赵琳璐副研究员，窦昆助理研究员，王蕊助理研究员，蒋童蒙助理研究员，均具有博士学位，国外人才引进 5 名，海南省百人专项人才计划 1 人；海南省南海青年名家 2 人；海南省高层次人才领军人才 1 人，拔尖人才 3 人，其它类高层次人才 2 人；海南省“515 人才工程”第二层次人选 1 人、第三层次人选 2 人。

研究方向

主要研究领域瞄准精准医学领域发展前沿，基于光学探针和生物材料的研发，整合荧光/拉曼多模态成像，在热带疾病可视化影像检测与精准治疗领域展开深入系统的研究，为疾病在热带条件下的发生和发展提供精准医疗数据和方案，研究方向聚焦疾病可视化诊断和治疗、多模式影像手术导航、即时检验（POCT）技术。推进产学研深度结合，促进基础研究

向临床转化。

申请人的研究紧紧围绕国家重大现实需求的热点、难点问题开展科研工作，面向地方和社会的重大需求，开展应用和对策研究。累计承担国家自然科学基金面上项目、国家自然科学基金青年项目、海南省高层次人才项目等研究课题 7 项。项目的实施推出了一批具前瞻性、指导性，并产生良好影响的科研成果。发表高水平论文 100 余篇。IF>10 论文 15 篇，IF 最高 54。论文总引 7500 余次。单篇最高引用 500 余次。引用超过 300 次的 7 篇，超过 100 次的 12 篇。H-index 43。专利发明授权 6 项，转化 2 项。系列工作的首创性得到了学术界同行的肯定，并在高水平期刊 *Accounts of Chemical Research*、*Angewandte Chemie* 和 *Nature Communications* 上专门评述，在学术界产生了较大影响。

在人才培养过程中突出学科交叉，带领团队推出的“新医科”医工结合新课程群，累计培养出优秀研究生 30 余名，为新医工结合提供良好的创新思路。专利的转化助力高新技术企业的发展。

主持过的项目

1、用于原位联动检测二硫化碳诱发生物活性小分子协同调控细胞信号转导的荧光探针及成像研究 国家自然科学基金委　2018.01-2022.12，65 万元

2、用于原位检测硫烷硫变化的荧光探针及成像研究　海南省科技厅　2020.01-2022.12，10 万元

3、构建荧光和拉曼光学探针用于恶性肿瘤可视化精准诊断的研究　海南省科技厅　2020.11-2022.11，60 万元。

发表的论文列表

1、Xiaoyu Zhang, Wangbo Qu , Heng Liu **, Yingying Ma , Linlin Wang ,Qi Sun*, Fabiao Yu*. Visualizing hydrogen sulfide in living cells and zebrafish using a redemitting fluorescent probe via selenium-sulfur exchange reaction , Analytica Chimica Acta, 2020, 1109, 37–43.

2、Chonggui Qiu, Ziyi Cheng, Chuanzhu Lv*, Rui Wang*, Fabiao Yu*. Development of bioorthogonal SERS imaging probe in biological and biomedical applications, Chinese Chemical Letters,2021,32, 2369–2379.

3、Xianzhu Luo, Ziyi Cheng, Rui Wang,* and Fabiao Yu*.Indication of Dynamic Peroxynitrite Fluctuations in the Rat Epilepsy Model with a Near-Infrared Two-Photon Fluorescent Probe，Analytical Chemistry, 2021, 93, 2490–2499.

4、Xiaofeng Wu, Rui Wang, Sujie Qi, Nahyun Kwon, Jingjing Han, Heejeong Kim, Haidong Li,Fabiao Yu,* and Juyoung Yoon*. Rational Design of a Highly Selective Near-Infrared Two-PhotonFluorogenic Probe for Imaging Orthotopic Hepatocellular Carcinoma Chemotherapy. Angewandte Chemie International Edition, 2021, 60, 15418-15425.

5、Ting Wang , Yanlong Xing** , Ziyi Cheng, Fabiao Yu*,Analysis of single extracellular

vesicles for biomedical applications with especial emphasis on cancer investigations,Trends in Analytical Chemistry,2022,152（116604）,0165-9936.

6、Hui Chen, Ziyi Cheng, Xuejun Zhou, Rui Wang,* and Fabiao Yu*,Emergence of Surface-Enhanced Raman Scattering Probes in NearInfrared Windows for Biosensing and Bioimaging, Analytical Chemistry,2022,94,143-164.

7、Shanshan Lin, Ziyi Cheng, Qifu Li,* Rui Wang,* and Fabiao Yu*, Toward Sensitive and Reliable Surface-Enhanced Raman Scattering Imaging: From Rational Design to Biomedical Applications ,Acs Sensors,2021,6,3912-3932.

8、Mingshun Li, Yanlong Xing, Yuxi Zoub, Guang Chena,*, Jinmao Youa,*, Fabiao Yua,b,*Imaging of the mutual regulation between zinc cation and nitrosyl via twophoton fluorescent probes in cells and in vivo, Sensors and Actuators B: Chemical,2020,309(127772),0925-4005.

9、Ji-Ting Hou, § Bingya Wang, § Yuxia Zou, § Peiwen Fan, Xueping Chang, Xinhua Cao,* Shan Wang,* and Fabiao Yu*,Molecular Fluorescent Probes for Imaging and Evaluation of Hypochlorite Fluctuations during Diagnosis and Therapy of Osteoarthritis in Cells and in a Mouse Model, Acs Sensors,2020,5,1949-1958.

10、Yan Wang, Feifei Yu, Xianzhu Luo, Mingshun Li, Linlu Zhao* and Fabiao Yu *,Visualization of carboxylesterase 2 with a near-infrared two-photon fluorescent probe and potential evaluation of its anticancer drug effects in an orthotopic colon carcinoma mice model, Chemical Communications,2020,56,4412-4415.

博士研究生

毕业证书

研究生　于法标　性别 男，一九八0 年 一 月 五 日生，于二0一0 年 九 月至 二0一三 年 十 月在　物理化学(含化学物理)专业学习，学制 3 年，修完博士研究生培养计划规定的全部课程，成绩合格，毕业论文答辩通过，准予毕业。

培养单位：　校(院、所)长：

证书编号：10141120130107007G　二0一三 年 十 月十二 日

中华人民共和国教育部学历证书查询网址：http://www.chsi.com.cn

博士学位证书

于法标　，男，1980年 1 月 5 日生。在　大连理工大学

物理化学(含化学物理)　学科（专业）已通过博士学位的课程考试和论文答辩，成绩合格。根据《中华人民共和国学位条例》的规定，授予 理学 博士学位。

校　　长

大连理工大学

学位评定委员会主席

二〇一三 年 十 月二十四日

证书编号：10141220130003 57

姓　　名：于法标

性　　别：男

出生年月：1980.01

身份证号码 327926198001056618

专业名称：临床检验学

资格名称：研究员

资格取得时间：2018年12月

证书编号：2019009

颁证单位：

发证日期：2019年1月20日

聘　书

LETTER OF APPOINTMENT

（2022）聘字29号

敬聘 于法标 同志为我校专业技术三级岗位，聘期从二〇二二年四月起至二〇二五年三月止。

海南医学院

二〇二二年四月

博士生导师聘书

DOCTORAL TUTOR APPOINTMENT

海医研聘[　　]　　号

敬聘　于法栋　为海南医学院　2019　级博士研究生指导教师。聘期自　2019　年9月起至　2022　年9月止。

海南医学院

2019年7月1日

聘　书

LETTER OF APPOINTMENT

于法标同志：

诚聘您为海南医学院第一附属医院客座教授。聘任期从2020年12月10日起至2023年12月10日止。

海南医学院第一附属医院

2020年12月10日

硕士生导师聘书

MASTER TUTOR APPOINTMENT

海医研聘[　　]　　号

敬聘　于法栋　为海南医学院 2019 级硕士研究生指导教师。聘期自 2019 年 9 月起至 2022 年 9 月止。

海南医学院

2019 年 7 月 1 日

聘　书

（2020）海医人聘字36号

敬聘于法标同志为我校临床检验学研究员，聘期从二０二０年一月起至二０二０年十二月止。

海南医学院人事处

二０二０年六月

证　书

经认定，于法标　（身份证号：372926198001056618）为海南省　领军人才。有效期　2019 年　3 月至　2022 年　3 月。

特发此证。

中共海南省委人才发展局

NO.HNRCL20190028

2019 年 3 月 15 日

证书

于法标同志：

经海南省委人才发展局、省农业农村厅、省工业和信息化厅、省财政厅、省教育厅、省卫生健康委员会、省科学技术厅、省社会科学界联合会、省科学技术协会批准，您入选为海南省“515人才工程”第二层次人选。

特发此证。

中共海南省委人才发展局（代章）

二〇二〇年一月二十五日

编号：第515-042014号

中共海南省委人才工作委员会办公室

琼人才办通〔2020〕9号

关于印发首批海南省“双百”人才团队名单的通知

各市、县、自治县党委组织部，省委各部门，省级国家机关各部门、各人民团体党组（党委），中央驻琼单位，各有关单位：

首批海南省“双百”人才团队（100个人才团队和100个储备人才团队）名单已经省委常委会审议通过，现印发给你们。请按《海南省人才团队建设实施办法（试行）》（琼人才通〔2020〕3号）第九款落实有关服务保障待遇。

附件：首批海南省“双百”人才团队名单

中共海南省委人才工作委员会办公室

2020年9月16日

（此件依申请公开）

序号	团队名称	依托单位名称	产业类型
52	热带地区新发再发传染病防控技术创新团队	海南省疾病预防控制中心	医疗健康
53	热带肿瘤诊治研究创新人才团队	海南省肿瘤医院	医疗健康
54	功能材料与分子影像技术创新团队	海南医学院	医疗健康
55	融易链区块链金融科技团队	海南易行企业管理咨询有限公司	现代金融
56	开放型经济理论与自贸港金融研究团队	海南大学	现代金融
57	中国特色自由贸易港工艺会展创新创业团队	三亚帝海狮王文化产业发展有限公司	会展业
58	海南旅投免税品物流供应链人才团队	海南省旅游投资发展有限公司	现代物流
59	自贸港跨境电商物流研究团队	海南师范大学	现代物流
60	中海油东方石化有限责任公司高层次人才团队	中海油东方石化有限责任公司	油气
61	海口奇力制药人才团队	海口奇力制药股份有限公司	医药
62	海南皇隆制药医药人才团队	海南皇隆制药股份有限公司	医药

海南省人才工作领导小组

琼人才通〔2018〕5号

关于印发2017年度海南省“百人专项”人选名单的通知

各市、县、自治县党委组织部、政府人力资源社会保障部门，省委各部门，省级国家机关各部门，各人民团体，部分国有企事业单位，有关单位：

现将2017年度海南省“百人专项”人选名单印发给你们。请按照《关于开展2017年海南省“百人专项”申报评审工作的通知》（琼人才办通〔2017〕30号）等文件规定，落实好相关支持和配套措施。

实施“百人专项”工程是贯彻省第七次党代会精神的重要举措，是落实《百万人才进海南行动计划（2018—2025年）》的重要要求，也是省委省政府关爱人才、培养人才、用好人才的重要途径。希望本次入选的高层次人才珍惜荣誉，立足本职岗位不忘初心、开拓创新，充分发挥好示范引领作用，

为加快推进海南全岛自由贸易试验区和中国特色自由贸易港做出更大贡献。

海南省人才工作领导小组

2018年6月28日

2017年度海南省“百人专项”人选名单

（按评审情况排序）

创新·实验室类（9人）

姓　名	工作单位
吴永忠	海南神农基因科技股份有限公司
严子梦	齐鲁制药（海南）有限公司
季秉清	齐鲁制药（海南）有限公司
王　宁	海南大学
王钦军	三亚中科遥感研究所
胡永华	中国热带农业科学院
王咸鹏	海南大学
廖　波	海南师范大学
郑作环	海南师范大学

重点学科类（10人）

姓　名	工作单位
曲　轶	海南师范大学
万迎朗	海南大学
高圣惕	海南大学
高艳安	海南大学
施海涛	海南大学
郭志强	海南大学
于法标	海南医学院

证书编号 20182010

证　书

于法标同志：

经省委批准，您被确定为海南省委联系服务重点专家后备人选。

特发此证。

中共海南省委人才工作委员会

项目余额表

报表期间:2022年06月

部门	项目	负责人	当前余额 项目结余
(1013)校领导	(SZD200007)构建荧光和拉曼光学探针用于恶性肿瘤	于法标	281,858.48
(1022)临床学院	(GKJ170024)用于原位联动检测二硫化碳诱发活性小分子协	于法标	64,643.77
(1022)临床学院	(SJK190003)用于识别肿瘤内多硫化物荧光探针的制备	于法标	2,893.82
(1022)临床学院	(SZR190037)用于原位检测细胞内硫烷硫变化的荧光探针	于法标	63,294.09
合计			412,690.16

报表日期 2022-06-22

3份

关于国家自然科学基金资助项目批准及有关事项的通知

于法标　先生/女士：

根据《国家自然科学基金条例》的规定和专家评审意见，国家自然科学基金委员会（以下简称自然科学基金委）决定批准资助您的申请项目。项目批准号：21775162，项目名称：用于原位联动检测二硫化碳诱发活性小分子协同调控细胞信号转导的荧光探针，直接费用：65.00万元，项目起止年月：2018年01月至2021年12月，有关项目的评审意见及修改意见附后。

请尽早登录科学基金网络信息系统（https://isisn.nsfc.gov.cn），获取《国家自然科学基金资助项目计划书》（以下简称计划书）并按要求填写。对于有修改意见的项目，请按修改意见及时调整计划书相关内容；如对修改意见有异议，须在计划书电子版报送截止日期前提出。**注意：请严格按照《国家自然科学基金资助项目资金管理办法》填写计划书的资金预算表，其中，劳务费、专家咨询费科目所列金额与申请书相比不得调增。**

计划书电子版通过科学基金网络信息系统（https://isisn.nsfc.gov.cn）上传，由依托单位审核后提交至自然科学基金委进行审核。审核未通过者，返回修改后再行提交；审核通过者，打印为计划书纸质版（一式两份，双面打印），由依托单位审核并加盖单位公章后报送至自然科学基金委项目材料接收工作组。计划书电子版和纸质版内容应当保证一致。

向自然科学基金委提交和报送计划书截止时间节点如下：

1、提交计划书电子版截止时间为**2017年9月11日16点**（视为计划书正式提交时间）；

2、提交计划书电子修改版截止时间为**2017年9月18日16点**；

3、报送计划书纸质版截止时间为**2017年9月26日16点**。

请按照以上规定及时提交计划书电子版，并报送计划书纸质版，未说明理由且逾期不报计划书者，视为自动放弃接受资助。

附件：项目评审意见及修改意见表

国家自然科学基金委员会

化学科学部

2017年8月17日

国家自然科学基金委员会

关于国家自然科学基金项目变更的通知

海南医学院 科研处:

根据你单位提出的关于 于法标 同志承担的国家自然科学基金项目（批准号：21775162）的变更申请，经审查，已做如下变更:

变更内容	变更前	变更后
受理编号	2177050073	
项目批准号	21775162	
申请人/项目负责人	于法标	
项目依托单位	中国科学院烟台海岸带研究所	海南医学院
研究期限	2018-01-01 至 2021-12-31	
项目组主要成员	王运庆，王文海，周娜，刘萍，韩潇玥，高敏，王悦，张霞	

特此通知。

国家自然科学基金委员会
化学科学部
2018年8月7日

海南省科学技术厅文件

琼科〔2019〕242号

海南省科学技术厅关于2019年海南省基础与应用基础研究计划（自然科学领域）高层次人才项目立项的通知

各有关单位:

经专家评审、公示、省科技厅审定，现将2019年海南省基础与应用基础研究计划（自然科学领域）高层次人才立项项目下达给你们，请抓紧做好项目的组织实施工作。现就有关事项通知如下:

一、请项目依托单位履行法人责任，组织好人力、物力和资金投入，完善所需条件，确保项目按计划实施。项目实施过程中涉及的实验动物、实验数据及政府采购等方面的事项，请按有关

规定执行。

二、项目管理和资金使用参照《海南省自然科学基金项目和经费管理办法》、《海南省财政科技计划项目经费管理办法》等有关规章制度执行，项目经费单独核算，专款专用。

三、请项目依托单位组织项目负责人登录省科技业务综合管理系统（http://218.77.186.200）填写项目任务书，项目实施起止时间为2020年1月1日至2022年12月31日。请于2020年1月15日24时前在线提交任务书，经省科技厅审核通过后，下载打印，并于2020年2月14日前将签章齐全的纸质项目任务书一式三份报送省科技厅413办公室。无正当理由逾期未报送任务书的视为自动放弃立项项目。

四、公开发表的论文、论著等请标注“2019年海南省基础与应用基础研究计划（自然科学领域）高层次人才项目基金资助”字样及项目批准号，未按规定标注的研究成果，验收时不予认可。

五、项目执行到期后，依托单位应当在项目实施期限届满后3个月内，将书面验收材料报省科技厅。无特殊原因到期未提交验收的项目，按“不通过验收”处理。

联系人：基础研究与重大专项处　蒙巍、朱科学

电　话：65339913、65343316

系统技术服务人员电话：4001616289

附件：2019年海南省基础与应用基础研究计划（自然科学领域）高层次人才立项项目表

海南省科学技术厅

2019年12月24日

（此件主动公开）

附件

2019年海南省基础与应用基础研究计划（自然科学领域）高层次人才立项项目表

金额：万元

序号	批准号	项目名称	依托单位	负责人	起止时间	资助经费
1	2019RC203	氧化石墨烯共载CpG及FGFR1-MIP-3a--PD1/Fc融合蛋白抗肿瘤免疫效应及机制研究	海南医学院	金剑峰	2020.1.1-2022.12.31	10
2	2019RC204	甲胎蛋白对肝癌细胞PD-L1表达的影响及其作用机制	海南医学院	李孟森	2020.1.1-2022.12.31	10
3	2019RC205	基于PI3K/Akt信号通路调控氧化应激探讨黎药-辣蓼干预胃粘膜损伤的作用机制	海南医学院	任守忠	2020.1.1-2022.12.31	10
4	2019RC206	基于机器视觉技术分析海南地区系统性红斑狼疮性肾病中医辨证分型及相关性研究	海南医学院	宫爱民	2020.1.1-2022.12.31	10
5	2019RC207	胆木抗溃疡生物碱的活性成分研究及其药效评价	海南医学院	李永辉	2020.1.1-2022.12.31	10
6	2019RC208	黎药来源-新木姜子碱靶向调控PTP1B改善IR的分子机制研究	海南医学院	张小坡	2020.1.1-2022.12.31	10
7	2019RC209	基于亲和素-生物素系统纳米肿瘤疫苗的构建及其临床前研究	海南医学院	张立明	2020.1.1-2022.12.31	10
8	2019RC210	用于原位检测细胞内硫烷硫变化的荧光探针及小鼠活体成像研究	海南医学院	于法标	2020.1.1-2022.12.31	10
9	2019RC211	定位于caveolae上的PMCA通过抑制nNOS活性调控乳鼠大肠ICC起搏活动	海南医学院	焦瀚仪	2020.1.1-2022.12.31	10
10	2019RC212	海南省气象灾害应急救护系统的改进及其效果研究	海南医学院	张华	2020.1.1-2022.12.31	10
11	2019RC213	抗CD16A双特异性抗体介导NK细胞抗病毒作用的研究	海南医学院	邵继平	2020.1.1-2022.12.31	10
12	2019RC214	碱促进构建1，2，3-三氮唑稠环化合物及其抗肿瘤活性研究	海南医学院	王雪松	2020.1.1-2022.12.31	10
13	2019RC215	基于水介质中多组分反应构筑吲哚类抗肿瘤小分子化合物研究	海南医学院	孔杜林	2020.1.1-2022.12.31	10
14	2019RC216	海南红树植物内生和根际放线菌的分离鉴定和α-葡萄糖苷酶抑制活性筛	海南医学院	隋金蕾	2020.1.1-2022.12.31	10
15	2019RC217	CpG胞外修饰ETs化全肿瘤细胞疫苗抗肿瘤作用研究	海南医学院	谭光宏	2020.1.1-2022.12.31	10
16	2019RC218	非人灵长类动物携带病毒的病毒组学及进化研究	海南医学院	杜江	2020.1.1-2022.12.31	10
17	2019RC219	番木瓜籽提取物异硫氰酸苄酯固体脂质纳米粒的制备、评价及抗假丝酵母菌活性的研究	海南医学院	何小稳	2020.1.1-2022.12.31	10
18	2019RC220	表面增强拉曼-近红外二区荧光双模态探针在肝癌精确诊断及光热治疗中的应用	海南医学院	王锐	2020.1.1-2022.12.31	10
19	2019RC221	基于茚分子修饰发夹探针指数放大荧光信号检测DENV的研究	海南医学院	邬强	2020.1.1-2022.12.31	10
20	2019RC222	益智仁改善力竭运动后心肌细胞凋亡的分子机制研究	海南医学院	徐百超	2020.1.1-2022.12.31	10

2019年海南省基础与应用基础研究计划（自然科学领域）
高层次人才立项项目表

金额：万元

序号	批准号	项目名称	依托单位	负责人	起止时间	资助经费
21	2019RC223	基于酿酒酵母全基因组扫描平台对六氟双酚A胁迫后相关功能基因的挖掘与机制研究	海南医学院	唐天乐	2020.1.1-2022.12.31	10
22	2019RC224	海南博鳌乐城国际医疗旅游先行区建设中的伦理与法律问题研究	海南医学院	苏玉菊	2020.1.1-2022.12.31	10
23	2019RC225	匹鲁卡品通过激动肝细胞M3受体影响lncRNA表达从而治疗肝损伤	海南医学院	刘艳	2020.1.1-2022.12.31	10
24	2019RC226	基于生物质固体废料纳米尺度的固相吸附剂-固相微萃取-色谱联用技术检测生物样品中的喹诺酮类抗生素的研究	海南医学院	温莹莹	2020.1.1-2022.12.31	10
25	2019RC227	热带假丝酵母菌多位点序列分型及其氟康唑耐药机制研究	海南医学院	吴金燕	2020.1.1-2022.12.31	10
26	2019RC228	脐静脉MSC源性外泌体经由AMPK/NLRP3通路保护脑血管内皮细胞缺氧损伤的作用研究	海南医学院	刘启兵	2020.1.1-2022.12.31	10
27	2019RC229	以甘草次酸为先导化合物的新型FXa抑制剂的设计、合成以及体外抗凝血活性和构效关系研究	海南医学院	王烁今	2020.1.1-2022.12.31	10
28	2019RC230	海南省丝盖伞属真菌新物种的发现与报道	海南医学院	范宇光	2020.1.1-2022.12.31	10
29	2019RC231	缩泉益肾方通过外泌体miRNA-572调节SOCS1/P21/Cyclin D1通路干预DN机制研究	海南医学院	尹德辉	2020.1.1-2022.12.31	10
30	2019RC232	COPD患者衰弱评估模型的构建与实证研究	海南医学院	张彩虹	2020.1.1-2022.12.31	10
31	2019RC233	海南热带媒介生物DNA条形码基因筛选及物种多样性研究	海南医学院	芦亚君	2020.1.1-2022.12.31	10
32	2019RC234	半细菌化类鼻疽伯克霍尔德杆菌为载体的肿瘤疫苗研究	海南医学院	黄风迎	2020.1.1-2022.12.31	10

索 引 号：00817378-2/2020-00365　　分　　类：公示公告/科技、教育

发文机关：省科学技术厅　　发文日期：2020年11月19日

名　　称：海南省科学技术厅关于2020年省重点研发计划拟立项项目的公示

文　　号：无　　主 题 词：无

各有关单位：

根据《海南省省级财政科技计划项目立项评审工作细则（试行）》的通知（琼科规（2020）7号）相关要求，按照公开申报、形式审查、专家评审等程序，经厅务会议、厅党组会议审议，2020年省重点研发计划拟支持223个项目，安排经费10482万元。

现将拟立项项目予以公示。任何单位和个人对公示内容如有异议，可在公示之日起5个工作日内（2020年11月19日-2020年11月25日），将加盖单位公章或签署个人真实姓名及联系方式的书面意见和相关材料提交省科技厅项目主管处室及审计与监督处。

联系人：

高新技术许克君，联系电话：65323068；

现代农业刘小霞，联系电话：65342626；

社会发展刘建勋，联系电话：66290357；

科技合作陈绍华，联系电话：65342482；

审计与监督处王学良，联系电话：65370256。

附件：2020年省重点研发计划拟立项项目表

海南省科学技术厅

2020年11月19日

（此件主动公开）

	三、社会发展方向			3982.00
102	以社区为基础的新发重大传染病预警、应对和运营优化	海南医学院	黄海溶	40.00
103	AI协同中小学生视功能筛查在近视防控中的应用	海口市人民医院	谢青	60.00
104	奇楠沉香中靶向GABAA激活作用的芳香类物质定向挖掘和镇静安神作用研究	中国医学科学院药用植物研究所海南分所	陈德力	40.00
105	院外心脏骤停普通公众急救培训关键技术研究及推广应用	海南医学院	颜时姣	20.00
106	基于孕妇血浆游离胎儿DNA高通量测序技术无创产前检测巴氏水肿胎的技术研发及应用研究	海口市妇幼保健院	符免艾	20.00
107	纳米偏光生物试剂盒在尿路上皮癌的应用研究	海南省人民医院	王阳	20.00
108	基于血管内皮细胞可视化高分子载体mRNA靶向干预放射性脑损伤的多模态MRI应用研究	海南省人民医院	陈旺生	40.00
109	利用互联网云技术精准构建海南省阿尔茨海默病网络化管理模式及应用与推广	海南医学院第二附属医院	曾超胜	20.00
110	KLF4对β-地中海贫血iPSC造血分化的影响	海南医学院	李崎	40.00
111	分泌型曲卷相关蛋白5在冠脉无复流中的作用及机制探讨	海南省人民医院	曾敏	40.00
112	凝血酶及其受体激活对心肌梗死后心功能影响的分子机制	海南医学院第一附属医院	唐利龙	80.00
113	AcCystatin/小胶质细胞/TNF-α轴介导广州管圆线虫感染所致小鼠神经元坏死性凋亡的机制研究	海南医学院	吕志跃	60.00
114	FOXA1对滋养细胞的调控及与子痫前期的相关性探讨	海南医学院第一附属医院	朱娟	20.00
115	恢复RhoE表达对糖尿病心肌病心功能保护的临床前研究	海南医学院	揭伟	40.00
116	铁死亡参与糖尿病心肌梗死的关键机制研究	中国人民解放军总医院海南医院	沈明志	60.00
117	海南省急性主动脉综合征诊疗技术的建立及其推广	海南医学院第二附属医院	王小敢	60.00
118	葡萄糖通过磷酸戊糖途径和Nrf2介导的氧化应激反应缓解百草枯中毒的研究	海南省人民医院	欧阳艳红	20.00
119	缺氧诱导因子在急性肾损伤至慢性肾脏病中的作用及机制研究	海南医学院第二附属医院	李冰	80.00
120	基于互联网的阻塞性睡眠呼吸暂停低通气综合征的家庭远程诊疗模式的建立与应用研究	三亚中心医院（海南省第三人民医院）	王配配	60.00
121	皮瓣血管增压技术在修复四肢大面积皮肤软组织缺损中的临床应用研究	海南医学院第二附属医院	胡朝波	20.00
122	外泌体介导的circ-PRKCH影响骨关节炎的分子机制	海口市人民医院	范忠诚	20.00
123	联合3D打印及组织工程技术构建精准中空支架诱导颗粒软骨再生成型及血管化重建乳头的研究	海南省人民医院	陈茹	20.00
124	从单细胞表达谱水平解析脐带间充质干细胞治疗卵巢早衰的分子机制及标准建立	海南省人民医院	包珊	40.00
125	胰腺癌中FoxM1-Smad4正反馈信号环路的建立及其靶向干预的临床前研究	海南医学院第一附属医院	郑少江	40.00
126	构建荧光和拉曼光学探针用于恶性肿瘤可视化精准诊断的研究	海南医学院	于法标	60.00
127	THOC2上调Wnt/β-catenin通路易化肝癌对仑伐替尼靶向耐药的研究	海南省人民医院	陈家诚	40.00
128	外泌体miR-92b-5p调控PTEN泛素化介导急性髓系白血病阿霉素耐药传递的分子机制及临床研究	海南医学院第一附属医院	姚晨姣	60.00
129	AID介导MMP14基因启动子去甲基化调控膀胱尿路上皮癌细胞EMT作用及机制的研究	海南医学院第一附属医院	梁培育	40.00

编号2022319

医药卫生科技文献
查收查引报告

委托咨询内容 收录引用证明

委托单位名称 海南医学院

委 托 人 于法标 电 话 17700917329

地址邮编 海口市学院路3号（571199）

检索单位名称 海南省医学信息研究所

受 理 人 李 琼 电 话 0898-66893774

地址邮编 海口市学院路3号（571199）

委托日期 2022年06月17日 报 告 日 期 2022年06月20日

检索结果：

根据本委托人的咨询要求，检索了美国《Web of Science 核心合集》，结果如下：

1. Visualizing hydrogen sulfide in living cells and zebrafish using a red-emitting fluorescent probe via selenium-sulfur exchange reaction

作者:Zhang, XY (Zhang, Xiaoyu); Qu, WB (Qu, Wangbo); Liu, H (Liu, Heng); Ma, YY (Ma, Yingying); Wang, LL (Wang, Linlin); Sun, Q (Sun, Qi); Yu, FB (Yu, Fabiao)

ANALYTICA CHIMICA ACTA 卷:1109 页:37-43 出版时间:MAY 1 2020

本文被《SCI》数据库收录，在《Web of Science》中总被引 19 次

期刊《ANALYTICA CHIMICA ACTA》影响因子 6.558（2020 年），中科院分区为“化学”大类 2 区、“分析化学”小类 1 区（2020 年公布）

2. Development of bioorthogonal SERS imaging probe in biological and biomedical applications

作者:Qiu, CG (Qiu, Chonggui); Cheng, ZY (Cheng, Ziyi); Lv, CZ (Lv, Chuanzhu) ; Wang, R (Wang, Rui); Yu, FB (Yu, Fabiao)

CHINESE CHEMICAL LETTERS 卷:32 期:8 页:2369-2379 出版时间:AUG 2021

本文被《SCI》数据库收录，在《Web of Science》中总被引 3 次

期刊《CHINESE CHEMICAL LETTERS》影响因子 6.779（2020 年），中科院分区为“化学”大类 2 区、“化学综合”小类 2 区（2021 年公布）

3. Indication of Dynamic Peroxynitrite Fluctuations in the Rat Epilepsy Model with a Near-Infrared Two-Photon Fluorescent Probe

作者:Luo, XZ (Luo, Xianzhu); Cheng, ZY (Cheng, Ziyi); Wang, R (Wang, Rui); Yu, FB (Yu, Fabiao)

ANALYTICAL CHEMISTRY 卷:93 期:4 页:2490-2499 出版时间:FEB 2 2021

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期刊《ANALYTICAL CHEMISTRY》影响因子 6.986（2020 年），中科院分区为“化学”大类 1 区、“分析化学”小类 1 区（2021 年公布）

4. Rational Design of a Highly Selective Near-Infrared Two-Photon Fluorogenic Probe for Imaging Orthotopic Hepatocellular Carcinoma Chemotherapy

作者:Wu, XF (Wu, Xiaofeng); Wang, R (Wang, Rui); Qi, SJ (Qi, Sujie); Kwon, N (Kwon, Nahyun); Han, JJ (Han, Jingjing); Kim, H (Kim, Heejeong); Li, HD (Li, Haidong); Yu, FB (Yu, Fabiao); Yoon, J (Yoon, Juyoung)

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5. Analysis of single extracellular vesicles for biomedical applications with especial emphasis on cancer investigations

作者:Wang, T (Wang, Ting); Xing, YL (Xing, Yanlong); Cheng, ZY (Cheng, Ziyi); Yu, FB (Yu, Fabiao)

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作者:Chen, H (Chen, Hui); Cheng, ZY (Cheng, Ziyi); Zhou, XJ (Zhou, Xuejun); Wang, R

(Wang, Rui; Yu, FB (Yu, Fabiao)

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7. Toward Sensitive and Reliable Surface-Enhanced Raman Scattering Imaging: From Rational Design to Biomedical Applications

作者:Lin, SS (Lin, Shanshan); Cheng, ZY (Cheng, Ziyi); Li, QF (Li, Qifu); Wang, R (Wang, Rui); Yu, FB (Yu, Fabiao)

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8. Imaging of the mutual regulation between zinc cation and nitrosyl via two-photon fluorescent probes in cells and in vivo

作者:Li, MS (Li, Mingshun); Xing, YL (Xing, Yanlong); Zou, YX (Zou, Yuxia); Chen, G (Chen, Guang); You, JM (You, Jinmao); Yu, FB (Yu, Fabiao)

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9. Molecular Fluorescent Probes for Imaging and Evaluation of Hypochlorite Fluctuations

during Diagnosis and Therapy of Osteoarthritis in Cells and in a Mouse Model

作者:Hou, JT (Hou, Ji-Ting); Wang, BY (Wang, Bingya); Zou, YX (Zou, Yuxia); Fan, PW (Fan, Peiwen); Chang, XP (Chang, Xueping); Cao, XH (Cao, Xinhua); Wang, S (Wang, Shan) ; Yu, FB (Yu, Fabiao)

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10. Visualization of carboxylesterase 2 with a near-infrared two-photon fluorescent probe and potential evaluation of its anticancer drug effects in an orthotopic colon carcinoma mice model

作者:Wang, Y (Wang, Yan); Yu, FF (Yu, Feifei); Luo, XZ (Luo, Xianzhu); Li, MS (Li, Mingshun); Zhao, LL (Zhao, Linlu); Yu, FB (Yu, Fabiao)

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Analysis of single extracellular vesicles for biomedical applications with especial emphasis on cancer investigations

Ting Wang [1], Yanlong Xing[**,1], Ziyi Cheng, Fabiao Yu[*]

Laboratory of Neurology, The First Affiliated Hospital of Hainan Medical University, Key Laboratory of Emergency and Trauma, Ministry of Education, College of Emergency and Trauma, Hainan Medical University, Haikou 571199, China

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A B S T R A C T

Extracellular vesicles (EVs) are lipid membrane enclosed nano-sized vesicles that are secreted by all known organisms. These vesicles are increasingly recognized as important circulating biomarkers for the diagnosis and prognosis of different diseases including various types of cancer, owing to their essential role in intercellular communication. EVs preserve heterogeneity in both physical properties and cargos, which makes it extraordinarily tough to fully exploit their clinical potential. Therefore, comprehensive characterization of single EVs and their sensitive detection are urgently demanded. In this article, we survey the latest progress in single EVs analysis with innovative discoveries in heterogeneity and highlight the various label-free and labelling approaches of single EVs detection. Furthermore, the state-of-the-art advances in single EV-detection based biomedical applications with especial emphasis on cancer investigations are summarized. To the end, the challenges and prospects for exploiting new system in the field of single EVs study are discussed.

1. Introduction

EVs are heterogenous, lipid-bilayer-phospholipid membranous vesicles generated by various living cells through active secretion [1,2]. Although initially thought to be cell debris, EVs have been discovered as vital biological species, owing to their physiological and pathological function in organisms. These vesicles carry bioactive molecules such as proteins and nucleic acids that are inherited from parental cells, and thus, affect microenvironment locally and at a distance by transferring cargos to recipient cells [3]. EVs can mediate intercellular communication and have been regarded as potential biomarkers for the diagnosis and treatment of diseases [4,5].

EVs can be released by cells to the extracellular space via different ways. Based on the currently known origin mechanism of EVs, these vesicles can be divided into three categories: exosomes (30–200 nm in diameter), microvesicles (100–1000 nm in diameter) and apoptotic bodies (500–2000 nm in diameter) [2]. In this review, we concern on exosomes and microvesicles and collectively define them as EVs. Exosomes and microvesicles have different modes of biogenesis. In one aspect, exosomes are originated from endocytic pathway. Initially, inward budding of cellular plasma membrane results in the formation of early endosome. Further inward invagination and budding of membrane inside early endosome leads to the formation of multivesicular body (MVB) bearing intraluminal vesicles that carry transmembrane, cytosolic contents, and peripheral proteins. MVBs may then partially fuse with lysosomes and degrades inside cell. Alternatively, MVBs can fuse with plasma membrane and release vesicles to the extracellular environment, which are defined as exosomes. In another aspect, the direct outward budding of the plasma membrane induces the formation of microvesicles [6,7]. Therefore, EVs preserve high heterogeneity in physical characteristics (size, density, morphology) and cargos (protein, lipid content, nucleic acids), mainly owing to their intricate biogenesis processes [8].

Growing evidence has demonstrated the role of EVs in the development of various diseases such as neurodegenerative diseases, acute organ injury and cancer, owing to the bioactive cargos carried and transferred by EVs [5]. In particular, tumour secreted EVs effect critical functions in facilitating intercellular communication in tumour microenvironment and modulate tumour initiation and progression [9]. Additionally, EVs are widely present in

* Corresponding author.
** Corresponding author.
E-mail addresses: xingyanlong@hainmc.edu.cn (Y. Xing), yufabiao@hainmc.edu.cn (F. Yu).
[1] These authors contributed equally to this work.

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Review

Development of bioorthogonal SERS imaging probe in biological and biomedical applications

Chonggui Qiu[1], Ziyi Cheng[1], Chuanzhu Lv*, Rui Wang*, Fabiao Yu*

The First Affiliated Hospital of Hainan Medical University, Key Laboratory of Emergency and Trauma, Ministry of Education, Key Laboratory of Hainan Trauma and Disaster Rescue, Institute of Functional Materials and Molecular Imaging, College of Pharmacy, College of Emergency and Trauma, Hainan Medical University, Haikou 571199, China

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ABSTRACT

Living-cell imaging demands high specificity, sensitivity, and minimal background interference to the targets of interest. However, developing a desirable imaging probe that can possess all the above features is still challenging. The bioorthogonal surface-enhanced Raman scattering (SERS) imaging has been recently emerged through utilizing Raman reporters with characteristic peaks in Raman-silent region of cells (1800–2800 cm^{-1}), which opens a revolutionary avenue for living-cell imaging with multiplexing capability. In this review, we focus on the recent advances in the technology development and the biological and biomedical applications of the living-cell bioorthogonal SERS imaging technique. After introduction of fundamental principles for bioorthogonal tag or label, we present applications for visualization of various intracellular components and environment including proteins, nucleic acids, lipids, pH and hypoxia, even for cancer diagnosis in tissue samples. Then, various bioorthogonal SERS imaging-guided therapy strategies have been discussed such as phototherapy and surgery. In conclusion, this strategy has great potential to be a flexible and robust tool for visualization detection and diseases diagnosis.

1. Introduction

The rapid detection and efficient therapy of diseases are very important for clinical medicine. However, the current methods for rapid detection and early treatment in clinical medicine cannot yet meet the clinical requirement. Therefore, it is an urgent need to develop analytical methods with rapid detection, low background inference and high sensitivity for biological and biomedical applications. In the past decades, the application of surface-enhanced Raman scattering (SERS) in biomedicine and medical transformation has attracted widespread interest from investigation of cellular function to cancer diagnosis and even *in vivo* detection [1]. On rough precious metal surfaces, the inelastic light scattering of molecules can be greatly enhanced (by factors up to 10^{14}-10^{15}). It shows the advantages of special biological detection: (1) high detection sensitivity with excellent detection limit even reaching pmol/L; (2) strong multi-component detection ability; (3) no aqueous solution background signal interference [2,3].

SERS theory has been studied by many scientists, in which two primary theoretical mechanisms have been developed including electromagnetic (EM) enhancement and chemical enhancement (CE). EM enhancement is commonly thought to make major contribution to the Raman signal enhancement [4,5]. When the light irradiates the surface of novel metal nanoparticles (NPs), it will induce collective oscillations from the NPs' surface electrons, which is known as surface plasmon resonance (SPR). When the incident light interacts with the plasmon, the dipolar field can be created with the exciting electric field. The phenomenon of redistribution of the local field induces a great enhancement of EM field at the specific position of the NPs as known as 'hot spot', which induced the enhanced Raman signals of the molecules located at hot spot. The EM enhancement mechanism cannot explain all the SERS phenomenon [6]. Then, CE mechanism has been proposed to explain why the Raman signal is enhanced by one or two orders of magnitude. CE involves the interaction between the adsorbed molecules and noble metal surface, which is mainly described in two ways [7]. The first explanation is that the charge intermediate induced by the interaction of molecules with the surface exhibits higher Raman scattering cross sections than that

* Corresponding authors.
E-mail addresses: lyuchuanzhu@hainmc.edu.cn (C. Lv), wangrui@hainmc.edu.cn (R. Wang), yufabiao@hainmc.edu.cn (F. Yu).
[1] These authors contributed equally to this work.

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analytical chemistry

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Emergence of Surface-Enhanced Raman Scattering Probes in Near-Infrared Windows for Biosensing and Bioimaging

Hui Chen,[‡] Ziyi Cheng,[‡] Xuejun Zhou, Rui Wang,* and Fabiao Yu*

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CONTENTS

The abnormal fluctuations of various biomarkers (such as intracellular nucleic acid, lipid, protein, pH, etc.) can be used as valuable diagnostic indicators for monitoring the physiological and pathological processes.[1−4] Traditional detection and imaging methods often face various deficiencies and new challenges. Thus, sensing and imaging techniques with properties such as having no contact, being in real-time, and having deep tissue penetration and high spatial resolution are urgently needed, which can display intrinsic chemical components in tissues and provide useful information for biomedical applications. In the past decades, surface-enhanced Raman scattering (SERS) has received more and more attention owing to its ultrahigh sensitivity and noninvasiveness.[5−7] As a powerful vibrational spectroscopic technique, SERS can provide useful information about the chemical structure and surrounding environment with an enhancement of up to single molecule level. Also, with a very narrow peak width, usually a few tenths of the fluorescence peak width, SERS makes multiplexing target detection in single excitation light possible.[8,9] In 1974, the SERS phenomenon was first discovered by Fleischmann and his colleagues when observing the Raman spectrum of pyridine molecules adsorbed on the surface of a rough silver electrode. During this process, the intensity of the Raman spectrum of the pyridine molecule on the electrode surface has been significantly improved compared to before. Moreover, the phenomenon has been developed as technique to detect the substances by identifying their specific Raman peaks, which has attracted extensive attention due to the greatly enhanced Raman signal of analyte. The mechanism of SERS signal enhancement mainly comes from two main theoretical mechanisms: electromagnetic enhancement (EM) and chemical enhancement (CE).[9] The coupling of localized surface plasmon resonance (LSPR) with incident light produces a secondary electric field around the plasmonic nanostructure, resulting in "hot spot", which is related to the composite, shape and size of the nanostructure. The molecule near or adsorbed on the metal surface will experience greatly enhanced Raman signal intensity. EM mode doesn't exhibit chemical-selectivity, providing the same enhancement for any type of molecule, which is distance-dependent. Only the molecule on or very close to the metal surface, the strong enhancement can be obtained. Since EM enhancement can't explain all the SERS phenomenon, the researchers then propose the CE mechanism. CE is acquired by enlarging the scattering cross−section of Raman reporters, which are grafted onto the plasmonic nanoparticles (NPs) with stable chemical bonds to generate SERS fingerprint signatures, and accounts for an enhancement up to two orders of magnitude. Therefore, the degree of enhancement depends on the metal substrate's electromagnetic properties and the Raman reporters' chemical properties.

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Imaging of the mutual regulation between zinc cation and nitrosyl *via* two-photon fluorescent probes in cells and *in vivo*

Mingshun Li[a], Yanlong Xing[b], Yuxia Zou[b], Guang Chen[a,*], Jinmao You[a,*], Fabiao Yu[a,b,*]

[a] The Key Laboratory of Life-Organic Analysis, Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, College of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, China

[b] Institute of Functional Materials and Molecular Imaging, Key Laboratory of Emergency and Trauma, Ministry of Education, Key Laboratory of Hainan Trauma and Disaster Rescue, College of Clinical Medicine, College of Emergency and Trauma, Hainan Medical University, Haikou 571199, China

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ABSTRACT

The homeostatic disorder of intracellular Zn^{2+} pool is closely associated with severe diseases. It has been reported that the high level of free Zn^{2+} during ischemia/reperfusion (I/R) process can result in oxidative stress damage on nerve cells. Given that nitrosyl (HNO) can aggravate the nerve injury during cerebral I/R process, we assume that there may exist a mutual regulation between Zn^{2+} and HNO under certain physiological conditions. To reveal this potential small-signaling-molecule crosstalk, we synthesized two-photon fluorescent probes **CHP-H** and **CHP-CH$_3$** to monitor intracellular Zn^{2+} in cell and mice hippocampus I/R models. The probes consist of two moieties: coumarin derivative as the two-photon fluorescence transducer, 2-hydrazino pyridine as the fluorescence modulator and Zn^{2+} chelator. Both probes exhibit excellent analytical properties for Zn^{2+} detection in simulated physiological systems. Utilizing **CHP-H** and an HNO probe **Cyto-JN**, we perform fluorescent imaging of cell I/R models. The results confirm that HNO can stimulate Zn^{2+} release from labile Zn^{2+} pool, whereas, the increase of intracellular Zn^{2+} cannot upregulate the level of HNO. Combining with the deep tissue imaging of mice hippocampus tissues, our probes may provide potential approaches for the medical diagnostic assessment of HNO regulation effect on Zn^{2+} release in clinical cerebral I/R-related diseases.

1. Introduction

As the second extensive transitional metal after iron in organism, zinc cation (Zn^{2+}) plays crucial roles in cells involving intracellular metabolism, apoptosis, enzymatic catalysis, neurotransmission, and so forth [1]. The total concentration range of Zn^{2+} pool in mammalian cells is approximately 100–500 μM, in particular, brain hippocampus is one of the most abundant distribution areas. The most fraction of intracellular Zn^{2+} is tightly chelated in metalloproteins, while the small portion is reserved through complexing with diverse small molecules, such as amino acids, for ready exchangeability. The free Zn^{2+} in cytoplasm has been involved in various signaling pathways that are relevant to different physiological and pathological events. For instance, in hippocampus, the variation in the homeostasis of Zn^{2+} is closely related to severe neurological diseases [2]. Zn^{2+} is involved in cerebral ischemia/reperfusion (I/R) injury and becomes a potentially toxic metal cation in brain. The neurotoxicity mechanism is that the abnormal levels of Zn^{2+} lead to oxidative stress and depolarization in mitochondria, as well as the inhibition of metabolic enzymes activity, and eventually activate apoptosis or necrosis processes in cells. Therefore, the significance of detecting Zn^{2+} is still drawing widespread interests [3].

Reactive nitrogen species (RNS), including nitric oxide (NO), peroxynitrite ($ONOO^-$), and nitrosyl (HNO), are associated with neurological diseases. NO and $ONOO^-$ can not only induce nitrosation of biothiols, but also stimulate the release of Zn^{2+} to trigger a range of zinc-related signal transduction pathway in cells [4,5]. HNO has been considered to be the form of single electron reduction and protonation of NO, which is biologically associated with the cardiovascular and nervous systems. HNO can aggravate the nerve injury during cerebral I/R process *via* oxidative stress. The injury eventually results in severe neurotoxicity and causes irreversible damage in neurons function [6]. Since Zn^{2+} and HNO simultaneously play roles in neuronal oxidative damage, we hypothesize that the intracellular Zn^{2+} may be associated with the intracellular HNO under a certain physiological or pathological state. However, the mutual regulations between Zn^{2+} and HNO

* Corresponding authors at: The Key Laboratory of Life-Organic Analysis, Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, College of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, China.

E-mail addresses: chenandguang@163.com (G. Chen), jmyou6304@163.com (J. You), fbyu@yic.ac.cn (F. Yu).

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Indication of Dynamic Peroxynitrite Fluctuations in the Rat Epilepsy Model with a Near-Infrared Two-Photon Fluorescent Probe

Xianzhu Luo, Ziyi Cheng, Rui Wang,* and Fabiao Yu*

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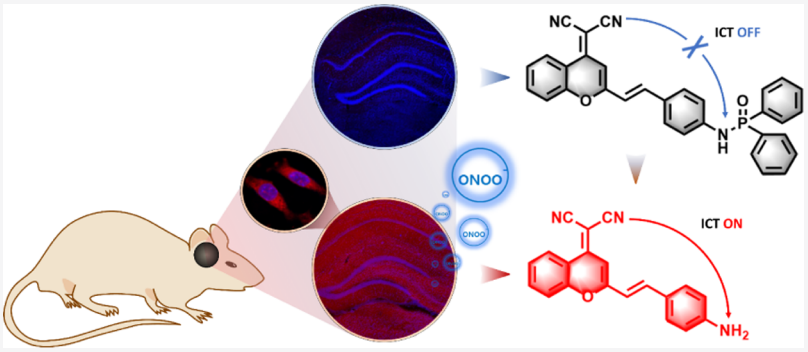

ABSTRACT: Epilepsy is a chronic neurodegenerative disease that has seriously threatened human health. Accumulating evidence reveals that the pathological progression of epilepsy is closely related to peroxynitrite ($ONOO^-$). Unfortunately, understanding the physiological roles of $ONOO^-$ in epilepsy is still challenging due to the lack of powerful imaging probes for the determination of the level of fluctuations of $ONOO^-$ in the epileptic brain. Herein, a near-infrared (NIR) two-photon (TP) fluorescent probe [dicyanomethylene-4*H*-pyran (DCM)−ONOO] is presented to trace $ONOO^-$ in living cells and in kainate (KA)-induced rat epilepsy models with satisfactory sensitivity and selectivity. The probe is composed of a NIR TP DCM fluorophore and a recognition moiety diphenylphosphinamide. The phosphoramide bond of the probe is interrupted after reacting with $ONOO^-$ for 10 min, and then, the released amino groups emit strong fluorescence due to the restoration of the intramolecular charge transfer process. The probe can effectively detect the changes of endogenous $ONOO^-$ with excellent temporal and spatial resolution in living cells and in rat epileptic brain. The imaging results demonstrate that the increasing level of $ONOO^-$ is closely associated with epilepsy and severe neuronal damage in the brain under KA stimulation. In addition, the low-dose resveratrol can effectively inhibit $ONOO^-$ overexpression and further relieve neuronal damage. With the assistance of TP fluorescence imaging in the epileptic brain tissue, we hypothesize that the abnormal levels of $ONOO^-$ may serve as a potential indicator for the diagnosis of epilepsy. The TP fluorescence imaging based on DCM−ONOO provides a great potential approach for understanding the epilepsy pathology and diagnosis.

INTRODUCTION

Epilepsy is a chronic neurodegenerative disease that causes transient brain dysfunction.[1] About 50 million people in the world suffer from epilepsy, which is growing at a rate of 2−5 in 10,000 per year. More and more anti-epileptic drugs have recently been developed; these anti-epileptic drugs are only intended to prevent seizures, but cannot prevent the occurrence of epilepsy and electrogenesis after status epilepticus.[2] The increasing evidence indicates that epilepsy is closely associated with oxidative stress following high levels of reactive oxygen/nitrogen species (ROS/RNS).[3] Therefore, in order to comprehensively understand the epilepsy disease, it is necessary to investigate the role of oxidative stress in the epilepsy disease.

As a complex physiological process, epileptic seizure involves oxidative stress and mitochondrial dysfunction, which is spontaneous, recurrent, and induces severe brain jury.[4] During the occurrence and development of epilepsy, the overexpressed ROS such as the superoxide anion ($O_2^{\bullet-}$) are continuously generated and immediately react with nitric oxide (NO) to produce $ONOO^-$, which results in irreversible damage to a series of biological targets, such as DNA, lipids, and proteins and further causes neuronal cell death.[5,6] Thus, the overexpressed $ONOO^-$ may be considered as an important indicator for the early diagnosis of epilepsy.[7] Unfortunately, the

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Article

Molecular Fluorescent Probes for Imaging and Evaluation of Hypochlorite Fluctuations during Diagnosis and Therapy of Osteoarthritis in Cells and in a Mouse Model

Ji-Ting Hou,[§] Bingya Wang,[§] Yuxia Zou,[§] Peiwen Fan, Xueping Chang, Xinhua Cao,* Shan Wang,* and Fabiao Yu*

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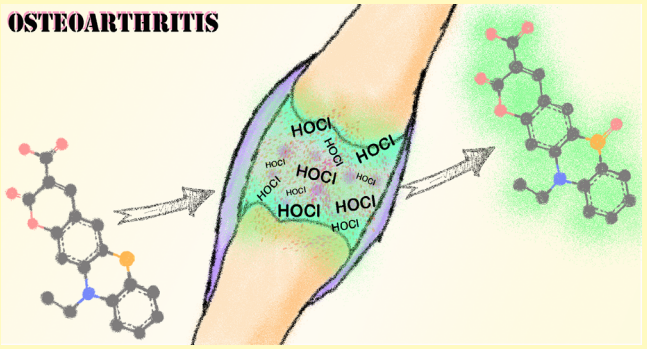
ABSTRACT: The early diagnosis of osteoarthritis (OA) can halt or delay the progression of the disease, and it is essentially beneficial to its treatment. However, biomarkers with sufficient sensitivity for dynamically identifying early OA are still yet to be determined. The overproduced hypochlorous acid (HOCl) has been proposed as an obvious symptom in early OA. Herein, based on the oxidation reaction of the sulfur atom in phenothiazine into sulfoxide, we design and synthesize a phenothiazine-derived coumarin fluorescent probe **PDC** for the detection of ClO^- in cells and in an OA mouse model. The probe **PDC** exhibits excellent selectivity and sensitivity for ClO^- detection with a limit of detection as low as 16.1 nM. Taking advantage of the probe **PDC**, we visualize and evaluate the level changes of ClO^- in macrophage cells, which is stimulated by various inflammatory factors. The anti-inflammatory and therapeutic effects of selenocysteine and methotrexate in inflamed cells are also confirmed. Finally, with in vivo imaging of ClO^- concentration changes in OA BALB/c mouse models, we successfully inspected the relationship between OA phenotypes and the burst of ClO^-. We suggest that abnormal changes in HOCl concentration may be considered as a new biomarker for the early OA diagnosis.



KEYWORDS: *fluorescent probe, hypochlorite, osteoarthritis, inflammation, mouse model*

INTRODUCTION

Osteoarthritis (OA) is a chronic and degenerative joint disorder in which articular cartilage injury and reactive hyperplasia of the joint edge and subchondral bone are involved owing to various risk factors, including aging, obesity, strain, trauma, and joint congenital abnormalities.[1,2] The structural abnormalities in joints are often accompanied by pain and joint dysfunctions, which severely impair the living quality of patients. However, OA is quite challenging to cure. As is well known, in the early stages of OA, articular cartilage is more metabolically adapted to its new environment, and the cartilage matrix is more easily repaired and regenerated than that at advanced stages of OA.[3,4] Therefore, the early diagnosis of OA have priority to hinder or prevent the progression of the disease, and it may be beneficial to the treatment. Magnetic resonance imaging (MRI) has been regarded as the most widely used imaging technique for clinical diagnosis of OA. Nevertheless, many structural abnormalities detected by MRI are very common in older populations, which may cause the diagnostic uncertainty for OA patients, and are not suitable for early diagnosis of OA.[5] Therefore, it is invaluable to exploit new biomarkers with sufficient sensitivity for identifying early OA.

It is now suggested that a low-grade inflammation is implicated in OA,[6,7] which induces the accumulation of neutrophils and macrophages in impaired joints. Then, myeloperoxidase (MPO), a specific enzyme, is overproduced in these cells. In patients with early OA, a 4-fold increase in MPO levels has been found in comparison with patients without OA or with advanced OA.[8] Accordingly, hypochlorous acid (HOCl, in this work mainly as ClO^-), a type of reactive oxygen species (ROS, generally including $^{\cdot}OH$, $O_2^{\cdot-}$, $ONOO^-$, $^1O_2$, ClO^-, and H_2O_2), is over-generated in early OA through an MPO-catalyzed reaction between H_2O_2 and Cl^-.[9] It is proposed that HOCl is involved in the degradative process of articular cartilage in early OA based on an indirect detection of

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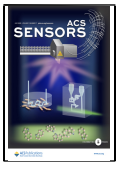

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Rational Design of a Highly Selective Near-Infrared Two-Photon Fluorogenic Probe for Imaging Orthotopic Hepatocellular Carcinoma Chemotherapy

Xiaofeng Wu[+], Rui Wang[+], Sujie Qi, Nahyun Kwon, Jingjing Han, Heejeong Kim, Haidong Li, Fabiao Yu, and Juyoung Yoon**

Abstract: *Selective fluorescence imaging of biomarkers in vivo and in situ for evaluating orthotopic hepatocellular carcinoma (HCC) chemotherapy remains a great challenge due to current imaging agents suffering from the potential interferences of other hydrolases. Herein, we observed that carbamate unit showed a high selectivity toward the HCC-related biomarker carboxylesterase (CE) for evaluation of treatment. A near-infrared two-photon fluorescent probe was developed to not only specially image CE activity in vivo and in situ but also target orthotopic liver tumor after systemic administration. The in vivo signals of the probe correlate well with tumor apoptosis, making it possible to evaluate the status of treatment. The probe enables the imaging of CE activity in situ with a high-resolution three-dimensional view for the first time. This study may promote advances in optical imaging approaches for precise imaging-guided diagnosis of HCC in situ and its evaluation of treatment.*

Introduction

Fluorescence imaging has been emerging as a powerful method for realizing the selective imaging of enzyme activity in vivo for accurate diagnosis, and therapy of cancer and evaluations of corresponding drug treatments because of its unique advantages, including good sensitivity and selectivity, in situ and/or real-time detection, high spatiotemporal resolution and noninvasive monitoring ability in living systems.[1] However, due to strong intrinsic light scattering in tissue, spatial resolution and penetration are rapidly compromised in imaging in vivo with depth. Near-infrared (NIR) two-photon (TP) fluorescence imaging is a promising tool for in vivo imaging of enzyme activity with decreased autofluorescence, high tissue penetration and resolution.[2]

Hepatocellular carcinoma (HCC) is a highly aggressive liver malignancy and a major cause of cancer-associated death.[3] An effective method is still urgently required for precisely diagnosing the condition of liver and evaluating drug treatments. In medicine, biomarkers can be tested in blood, tissue and body fluids as sign reflecting the normal or abnormal conditions, allowing the evaluating of individual treatment for cancer and detections of cancer at early stages.[4] Thus, given that carboxylesterase (CE) is an important biomarker of HCC, a selective and sensitive fluorescent probe for testing CE levels in vivo may be an effective tool for indicating the severity or presence of liver conditions.[5] As a mainstream approach for biomarker detection, the specificity of serum assays may be impaired due to biomarkers or interference in the multiple organs or tissues in addition to the disease lesions.[6] Biomarker analysis at a specific origin can more accurately reflect the real condition of the liver under drug treatment. In addition, an ideal method for testing biomarkers ought to have higher selectivity.[4b]

Thus, an activatable and highly selective NIR TP fluorescent probe for localizing spatially and elevating CE levels in the original hepatic organ is rather important and meaningful for better accurate imaging-guided diagnosis of the orthotopic HCC and its evaluation of treatments. As an indispensable element of fluorescent probes, recognition moieties are extremely responsible for selective and sensitive interactions with enzymes of interest.[7] However, currently, ester bonds such as acetyl units are still employed as a main recognition moiety for constructing fluorescent probes for CE activity besides butyrylcholinesterase (BChE) and acetylcholinesterase (AChE), resulting in potential mutual interferences.[8] This may seriously compromise the accurate measurement of CE activity in vivo and in situ. This great challenge encourages us to engineer a selective recognition moiety for constructing a NIR TP fluorescent probe for imaging the CE. Fortunately, we noticed that rivastigmine and physostigmine (commercial inhibitors of BChE and AChE) contain carbamate moieties that can function to inhibit the activity of BChE and AChE (Scheme 1 A).[9] However, irinotecan (CPT-11) as a precursor of an anticancer drug containing a carbamate unit could be a substrate catalyzed by CE to release anticancer SN38 (Scheme 1 A and Figure S1).[10] This indicates that compounds containing carbamate units

[*] Dr. X. Wu,[+] S. Qi, Dr. N. Kwon, J. Han, H. Kim, Dr. H. Li, Prof. Dr. J. Yoon
Department of Chemistry and Nanoscience, Ewha Womans University
Seoul 03706 (Republic of Korea)
E-mail: jyoon@ewha.ac.kr
Dr. R. Wang,[+] Prof. Dr. F. Yu
Key Laboratory of Emergency and Trauma, Ministry of Education, Key Laboratory of Hainan Trauma and Disaster Rescue, The First Affiliated Hospital of Hainan Medical University, Institute of Functional Materials and Molecular Imaging, College of Emergency and Trauma, Hainan Medical University
Haikou 571199 (China)
E-mail: yufabiao@hainmc.edu.cn
[+] These authors contributed equally to this work.
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Review

Toward Sensitive and Reliable Surface-Enhanced Raman Scattering Imaging: From Rational Design to Biomedical Applications

Shanshan Lin,[#] Ziyi Cheng,[#] Qifu Li,[*] Rui Wang,[*] and Fabiao Yu[*]

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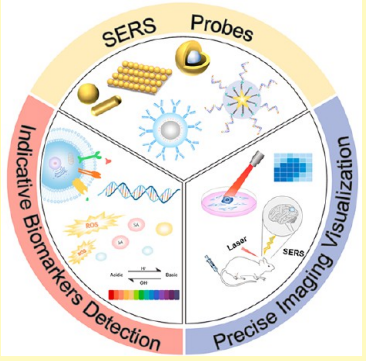
ABSTRACT: Early specific detection through indicative biomarkers and precise visualization of lesion sites are urgent requirements for clinical disease diagnosis. However, current detection and optical imaging methods are insufficient for these demands. Molecular imaging technologies are being intensely studied for reliable medical diagnosis. In the past several decades, molecular imaging with surface-enhanced Raman scattering (SERS) has significant advances from analytical chemistry to medical science. SERS is the inelastic scattering generated from the interaction between photons and substances, presenting molecular structure information. The outstanding SERS virtues of high sensitivity, high specificity, and resistance to biointerference are highly advantageous for biomarker detection in a complex biological matrix. In this work, we review recent progress on the applications of SERS imaging in clinical diagnostics. With the assistance of SERS imaging, the detection of disease-related proteins, nucleic acids, small molecules, and pH of the cellular microenvironment can be implemented for adjuvant medical diagnosis. Moreover, multimodal imaging integrates the high penetration and high speed of other imaging modalities and imaging precision of SERS imaging, resulting in final complete and accurate imaging outcomes and exhibiting robust potential in the discrimination of pathological tissues and surgical navigation. As a promising molecular imaging technology, SERS imaging has achieved remarkable performance in clinical diagnostics and the biomedical realm. It is expected that this review will provide insights for further development of SERS imaging and promote the rapid progress and successful translation of advanced molecular imaging with clinical diagnostics.



KEYWORDS: *surface-enhanced Raman scattering (SERS), SERS probes, optical sensors, SERS imaging, molecular imaging, biomarker detection, biomedical applications, medical diagnosis*

Precise clinical diagnosis in the early stage is of great significance for follow-up timely clinical decision making and survival status. Conventional clinical laboratory diagnostic detection based on indicative biomarkers through *in vitro* detection can be used to characterize the occurrence and progress of diseases, while delineation of the boundaries of diseases is ignored and can only be achieved with a series of large-scale imaging instruments.[1] Molecular imaging is a collective concept that allows visualization and quantitative characterization for biological functions and cell activities through specific molecules in the subcellular dimension.[2,3] Along with the development of rational contrast agents of organic molecules and nanoparticles, targeting imaging detection with specific biomarkers can be achieved.[4,5] Molecular imaging methods have great potential in medicine for accurate diagnosis, measuring the severity of diseases and guiding surgeries for personalized treatment, such as fluorescent imaging, computer tomography (CT), positron emission computed tomography (PET-CT), magnetic resonance imaging (MRI), and Raman scattering.[6−8] However, both CT and PET produce ionizing radiation to organisms, and even PET is costly; easy photobleaching and unspecific autofluorescence emanating from biological tissue components are the two main inherent defects of fluorescent imaging technology. Compared to these imaging techniques, Raman scattering can overcome most of the obstacles above. The individual Raman spectra peak representing specific molecular vibrational information has less overlap than fluorescence peaks, allowing for multitarget applications. Features of light bleaching resistance and noninvasiveness also make Raman scattering more suitable for wide applications in disease diagnostic fields. In addition, surface-enhanced Raman scattering as a specific spectrum technology can be conducted for targeted biomarkers in a wide range of detection media, both *in vitro* detection in plasma and urine and *in vivo* detection in live cells and tissues.

The Raman scattering effect, first discovered by Raman and Krishnan in 1928, is a kind of inelastic scattering caused by

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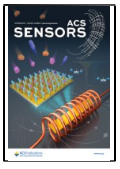

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Visualization of carboxylesterase 2 with a near-infrared two-photon fluorescent probe and potential evaluation of its anticancer drug effects in an orthotopic colon carcinoma mice model†

Yan Wang,[ab] Feifei Yu,[b] Xianzhu Luo,[ab] Mingshun Li,[ab] Linlu Zhao*[b] and Fabiao Yu *[ab]

We establish a near-infrared two-photon fluorescent probe for the detection of CE2 with high selectivity and sensitivity. This probe exhibits low cytotoxicity and superior tissue penetration ability for evaluating the real-time activity of CE2 in living cells, in cancer tissues, and in a colon carcinoma mice model.

Carboxylesterases (CEs), a component of α/β hydrolase fold protein, play pivotal roles in the hydrolysis of substances containing esters, amides, carbamates and thioesters.[1–4] CE2, a major isoform of CEs, is found to be highly expressed in many cancer cells and mediates the activation process of many prodrugs such as gemcitabine, irinotecan (CPT-11) and capecitabine (CAPE).[5,6] Therefore, the individual differences in the CE2 activity have been closely associated with the cytotoxicity and efficacy of the relevant clinical anticancer drugs.[7] Furthermore, CE2 is considered to be the essential determinant in intestinal first-pass metabolism, especially for oral anticancer prodrugs.[8] In view of the critical roles of CE2 in metabolism of various anticancer prodrugs, it is quite necessary to develop suitable techniques for accurate and sensitive detection of CE2 under complex physiological conditions.

Several effective methods for evaluating the CE2 activity have been established.[9,10] However, these technical methods usually involve time-consuming and complex procedures, high cost, and skilled operators, which may largely restrict their application in rapid detection. As attractive alternatives, fluorescent probes have become indispensable tools toward exploring bioactive molecules.[11–13] Although small-molecule based fluorescent probes have been synthesized and utilized for the detection of CE2 *in vitro* and *in vivo*,[14–16] few probes are competent for practical applications mainly due to their relatively short excitation/emission wavelength at which there is strong intrinsic autofluorescence background from living tissues. This issue greatly restricts the deep-tissue penetration and measurement accuracy under physiological conditions. Compared to the single-photon confocal imaging, the developed two-photon (TP) microscopy features the ability to avoid biological autofluorescence and to reduce photodamage, because the near-infrared (NIR) wavelength can achieve a deeper penetration and can exhibit a higher 3D temporal spatial resolution.[17–20] Hence, a two-photon fluorescent probe has attracted extensive research interest in sensing of bioactive macromolecule CE2 in sophisticated living systems. However, there still exist obstacles of the TP probes, which mainly lie in the deficiency with emission wavelength since most of these TP probes only can emit fluorescence at short wavelength (<550 nm).[21] This issue may fail the practical bio-imaging especially in deep tissues as the collection efficiency of fluorescence signals will be greatly decreased, further affecting the sensing accuracy and sensitivity of TP probes.[22,23] Therefore, it is of great significance to develop TP probes with excitation/emission wavelength in the NIR region[21] which can not only minimize background fluorescence interference owing to reducing absorption by bio-molecules but also achieve deeper penetration to facilitate the precise detection of CE2 in living systems.

As illustrated in Scheme 1, the overall design strategy of the probe **DCM-CES2** was based on the attachment of an enzyme-active moiety L-leucine to an excellent NIR TP chromophore dicyanomethylene-4*H*-pyran (DCM),[11,13,24] because it showed large Stokes shifts and NIR emission (>650 nm). Since the CE2 could specifically hydrolyze the compound with large alcohol and small acyl group, our probe **DCM-CES2** was able to serve as a highly selective substrate for CE2. The detailed synthetic route is shown in the ESI.† The compounds were characterized by ^{1}H NMR, ^{13}C NMR and HR-MS.

We inspected the spectral characteristics of the probe **DCM-CES2** under simulated physiological conditions (PBS buffer pH = 7.4, 10 mM at 37 °C). As shown in Fig. 1a, the probe **DCM-CES2**

[a] *The Key Laboratory of Life-Organic Analysis, Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, College of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, China*
[b] *Institute of Functional Materials and Molecular Imaging, Key Laboratory of Emergency and Trauma, Ministry of Education, College of Pharmacy, Key Laboratory of Hainan Trauma and Disaster Rescue, College of Clinical Medicine, College of Emergency and Trauma, Hainan Medical University, Haikou 571199, China. E-mail: fbyu@yic.ac.cn, zhaolinlu@hainmc.edu.cn*

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Visualizing hydrogen sulfide in living cells and zebrafish using a red-emitting fluorescent probe via selenium-sulfur exchange reaction

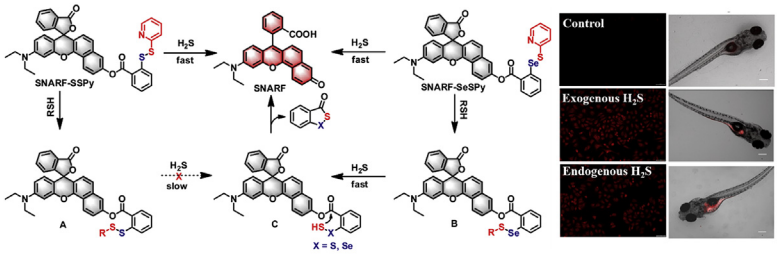
Xiaoyu Zhang [a, c, 1], Wangbo Qu [c, 1], Heng Liu [a, c, **], Yingying Ma [c], Linlin Wang [c], Qi Sun [b, ***], Fabiao Yu [a, *]

[a] Institute of Functional Materials and Molecular Imaging, Key Laboratory of Emergency and Trauma, Ministry of Education, Key Laboratory of Hainan Trauma and Disaster Rescue, College of Clinical Medicine, College of Emergency and Trauma, Hainan Medical University, Haikou, 571199, China
[b] Key Laboratory for Green Chemical Process of Ministry of Education and School of Chemistry and Environmental Engineering, Wuhan Institute of Technology, Wuhan, 430205, China
[c] Hubei Collaborative Innovation Center for Advanced Organic Chemical Materials, Ministry of Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules & College of Chemistry and Chemical Engineering, Hubei University, Wuhan, 430062, China

HIGHLIGHTS

- Two red-emitting fluorescent probes SNARF-SSPy and SNARF-SeSPy have been designed for efficient detection of H_2S.
- By comparing the two probes, only SNARF-SeSPy exhibited excellent anti-interference even in the presence of high concentration of thiols.
- Results of imaging H_2S in living cells and zebrafish demonstrated that SNARF-SeSPy could be employed to track exogenous and endogenous H_2S in vitro and in vivo.

GRAPHICAL ABSTRACT



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ABSTRACT

Hydrogen sulfide (H_2S) is an important endogenous gasotransmitter and has been implicated with a variety of biological processes. The development of an efficient method for monitor H_2S fluctuations in biological systems is of great significance to understand its roles in physiological and pathological conditions. In this work, two red-emitting fluorescent probes SNARF-SSPy and SNARF-SeSPy for H_2S detection with turn-on fluorescence signals were reported. Interestingly, SNARF-SeSPy exhibited excellent anti-interference via dual selenium-sulfur exchange reaction even in the presence of high concentrations of thiols, whereas SNARF-SSPy did not sense H_2S in the same condition. Additionally, in the present of H_2S, SNARF-SeSPy showed a rapid response and excellent sensitivity with a detection limit of

* Corresponding author.
** Corresponding author. Institute of Functional Materials and Molecular Imaging, Key Laboratory of Emergency and Trauma, Ministry of Education, Key Laboratory of Hainan Trauma and Disaster Rescue, College of Clinical Medicine, College of Emergency and Trauma, Hainan Medical University, Haikou, 571199, China.
*** Corresponding author.
E-mail addresses: liuheng11b@hubu.edu.cn (H. Liu), qisun@wit.edu.cn (Q. Sun), fbyu@yic.ac.cn (F. Yu).
[1] These two authors contributed equally to this work (X. Y. Zhang and W.B. Qu).

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