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Intravascular NIRF Molecular Imaging Approaches in Coronary Artery Disease

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Abstract Progression of vulnerable coronary atherosclerotic plaques underlies most episodes of acute myocardial infarction and sudden cardiac death. Recent advances in biological/molecular imaging technology are now enabling the accurate identification of high-risk plaques and coronary stents in living subjects. Due to their smaller caliber and susceptibility to cardiorespiratory motion, noninvasive molecular imaging of human coronary arteries remains challenging. Therefore, intravascular high-resolution molecular imaging approaches appear necessary to resolve molecular features of human coronary arteries and stents. Here we present recent progress in intravascular near-infrared fluorescence (NIRF) molecular imaging, including the evolution from stand-alone NIRF systems to those integrated with structural imaging methods including optical coherence tomography and intravascular ultrasound. Preclinical demonstrations of imaging inflammation, fibrin, and endothelial impairment are highlighted. We then close with a discussion of translation of NIRF imaging to the cardiac catheterization laboratory and showcase first-in-human intracoronary imaging results of NIR autofluorescence in CAD.

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Introduction

Consequences of coronary artery disease (CAD) including myocardial infarction and sudden cardiac death typically occur from obstructive atherosclerotic plaque formation, progression, and complication. Based on the vulnerable plaque hypothesis, namely that accurate identification of high-risk plaques could guide and/or enhance pre-emptive therapy, a wealth of imaging studies have been undertaken to identify predictive features of high-risk plaques. In particular, studies employing intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have provided high-resolution images of coronary artery disease. These technological advances in intravascular imaging have provided substantial insights into the natural history of coronary artery plaque (plaque burden, progression/regression, positive/negative remodeling, for example). A recent natural history study employing IVUS-virtual histology showed the ability to predict high-risk plaque progression, to a modest extent [1]. However, IVUS and OCT approaches are currently not sufficiently accurate for routine clinical use, and currently provide scant information regarding the biological features of atherosclerotic plaques.

In contrast to the intense focus on structural characteristics underlying high-risk, or vulnerable plaques, much less understanding of the in vivo biology of CAD has been elucidated in clinical subjects. Understanding the molecular mechanisms of coronary artery disease and their role in predicting plaque rupture, the major cause of myocardial infarction, is highly desirable. In the last decade, significant advances in noninvasive molecular imaging of human atherosclerosis have

occurred, in particular via PET- and MRI-based reporter agents [2–4]. However, due to resolution and sensitivity considerations, most applications have been in the larger arteries, such as the carotid arties and the aorta.

In contradistinction, human coronary molecular imaging demonstrations have remained elusive, primarily due their smaller size (2–4 mm diameter) and vulnerability to complex cardiorespiratory motion that limit noninvasive imaging approaches. To address this unmet need, high-resolution intravascular molecular imaging approaches appear necessary. One promising approach is intravascular near-infrared fluorescence (NIRF) imaging, an optical-based approach that utilizes NIR light to excite targeted or activatable fluorophores that illuminated specific molecules, cells, or biological processes [2–4]. Here we detail the progress of intravascular NIRF imaging in illuminating the biology of high-risk plaques and high-risk stents, and showcase the translation of NIRF systems and agents towards human clinical application.

Intravascular NIRF Imaging Systems

Standalone NIRF Imaging

One-Dimensional Intravascular NIRF Sensing

In 2008, a novel first-generation one-dimensional (1D) NIRF sensing catheter was developed and tested the feasibility of detecting NIRF signals in living subjects [5]. This system was based on a clinical OCT guidewire, with laser modification to 750-nm NIR excitation. In a rabbit model of atherosclerosis, this guidewire was advanced to a diseased iliac artery under fluoroscopic guide, then catheter was manually pulled back to detect the local NIRF signal at atherosclerotic plaque (Fig. 1). The NIRF signal indicated augmented cathepsin protease activity, a mediator of plaque expansion via collagenolytic and elastinolytic actions. Cathepsin activity was detected by intravenous injection of a protease-activatable NIRF molecular imaging agent, Prosense/VM110, 24 h prior to imaging. This early experiment demonstrated the feasibility of intravascular NIRF sensing catheter to detect local NIRF activity within the living subjects, without the need for blood flushing. However, this prototype catheter was not capable of detecting the full 360° circumference of vessels, resulting in imaging of only approximately one eighth of the vessel wall.

Two-Dimensional Intravascular NIRF Imaging

In 2012, a second-generation two-dimensional (2D) NIRF imaging system was developed [6]. This second-generation system provided additional capabilities of automated pullback and rotation, allowing full 360° intravascular NIRF imaging of the artery. Manual co-registration of intravascular 2D NIRF and IVUS anatomical images was enabled by radiopaque markers and arterial fiducials such as side branches. The NIRF-IVUS fusion maps identified inflamed plaque regions illuminated by Prosense/VM110 (Fig. 2) in rabbit iliac arteries and the larger diameter aorta, through blood, without the need for flushing. This approach offered additional molecular imaging information such as inflammatory activity in conjunction with anatomical IVUS or OCT images. A limitation of this catheter was the need for separate imaging of IVUS or OCT to obtain anatomical information, and the inability to exactly identify the position of the NIRF catheter within the lumen. The latter limitation prohibited distance-based compensation of the NIRF signal (catheter-to-artery wall distance), which is necessary as the NIRF signal is fundamentally surface weighted and depends on the amount of blood or saline between the NIRF catheter and the artery wall. Separate imaging devices also precluded exact co-registration of IVUS and NIRF in the angular dimension (0–360° axis).

Integrated NIRF Molecular and Structural Imaging

NIRF-OCT Imaging

To allow simultaneous molecular and microstructural imaging, and to enable distance-based compensation of the NIRF signal, a third-generation combined NIRF-OCT system was engineered. The OCT and NIRF illumination light sources and signal receptions were combined via a specialized dual-modality rotary junction. The integrated system enabled simultaneous imaging of microstructural images by OCT and biological/molecular imaging by NIRF, in a single pullback in vivo [7]. Due to blood attenuation of OCT signals, imaging was performed in saline, following displacement of blood. The integrated imaging catheter provided precisely co-registered OCT and NIRF images. Integrated NIRF-OCT imaging successfully visualized the inflammatory protease activity in atherosclerotic plaque by Prosense/VM110 and the OCT-provided anatomical images in vivo. Ex vivo NIRF imaging and histological analyses confirmed the accuracy of the in vivo NIRF-OCT results. In addition, as OCT has excellent high-resolution imaging capabilities, NIRF-OCT was utilized to image coronary stent detail in vivo. After coating of a coronary stent with a Cy7-labeled peptide targeted to fibrin (Cy7 = NIR fluorophore), the stent was implanted into a rabbit iliac artery, followed by in vivo NIRF-OCT imaging. Regions of the stent containing thrombi identified by OCT also showed Cy7-fibrin signal by NIRF imaging (Fig. 3). However, NIRF molecular imaging detected fibrin stent signals that was not detected by stand-alone OCT as confirmed by histological assessment, indicating that NIRF-OCT fibrin imaging offers improved sensitivity beyond stand-alone OCT.

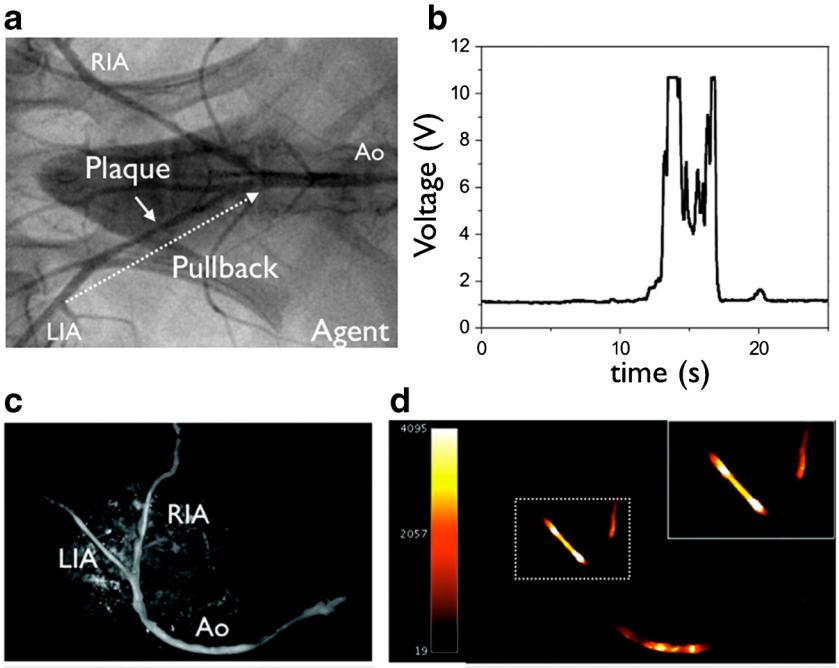

Fig. 1 First-generation intravascular NIRF sensing catheter. **a** An intravascular NIRF sensing catheter was advanced into left iliac artery (LIA) under the fluoroscopic guidance, followed by manual pullback (dotted arrow). **b** A cathepsin protease activity NIRF sensor, Prosense/VM110, was injected 24 h before the imaging into the rabbit with atherosclerotic plaque. Elevated NIRF signal was observed on pullback in iliac atherosclerotic legions. **c** Ex vivo white light and **d** NIRF images of atherosclerotic arteries. Strong NIRF signal was detected in diseased legions. Minimal NIRF signal was observed in saline-injected control rabbits (data not shown). *RIA* right iliac artery, *LIA* left iliac artery, *Ao* aorta. Reproduced by permission from Wolters Kluwer Health, Inc., from Reference [5], Jaffer FA, Vinegoni C, John MC et al. Real-time catheter molecular sensing of inflammation in proteolytically active atherosclerosis. Circulation 2008;118:1802–9

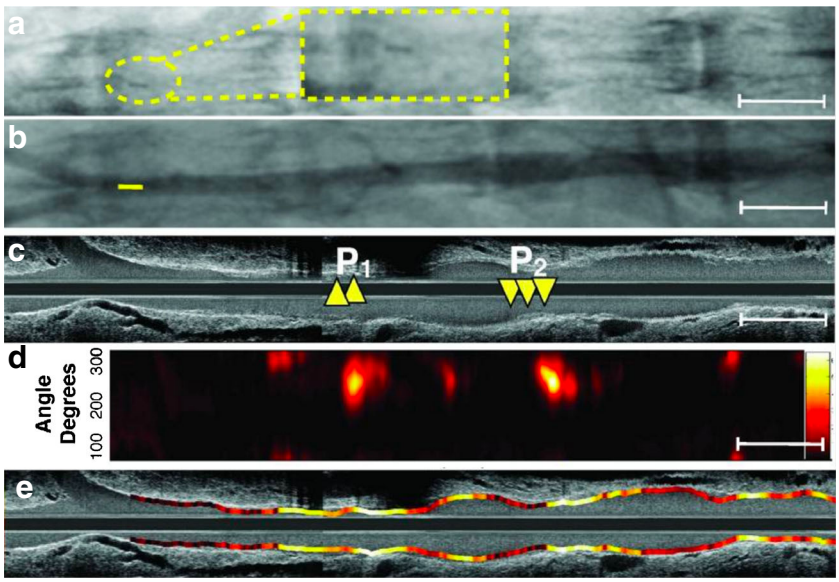

Fig. 2 Two-dimensional intravascular NIRF imaging. **a** Localization of the radiopaque tip of an automated rotational and translational NIRF imaging catheter by fluoroscopy. The tip of the catheter is visible on fluoroscopy (*dotted circle*, and magnified in *dotted square*). **b** Angiography of an atherosclerotic rabbit aorta. Pullback of the NIRF catheter beginning at the iliac bifurcation. **c** A longitudinal IVUS image shows the localization of atherosclerotic plaque (*arrow*, P1–P2). **d** Two-dimensional NIRF image aligned with angiogram and IVUS image demonstrates high NIRF signal localized to the edge of IVUS-detected atherosclerotic plaque. **e** Merged longitudinal IVUS/NIRF image. Modified by permission from Elsevier from Reference [6], Jaffer FA, Calfon MA, Rosenthal A et al. Two-dimensional intravascular near-infrared fluorescence molecular imaging of inflammation in atherosclerosis and stent-induced vascular injury. J Am Coll Cardiol 2011;57:2516–26. Permission conveyed through Copyright Clearance Center, Inc

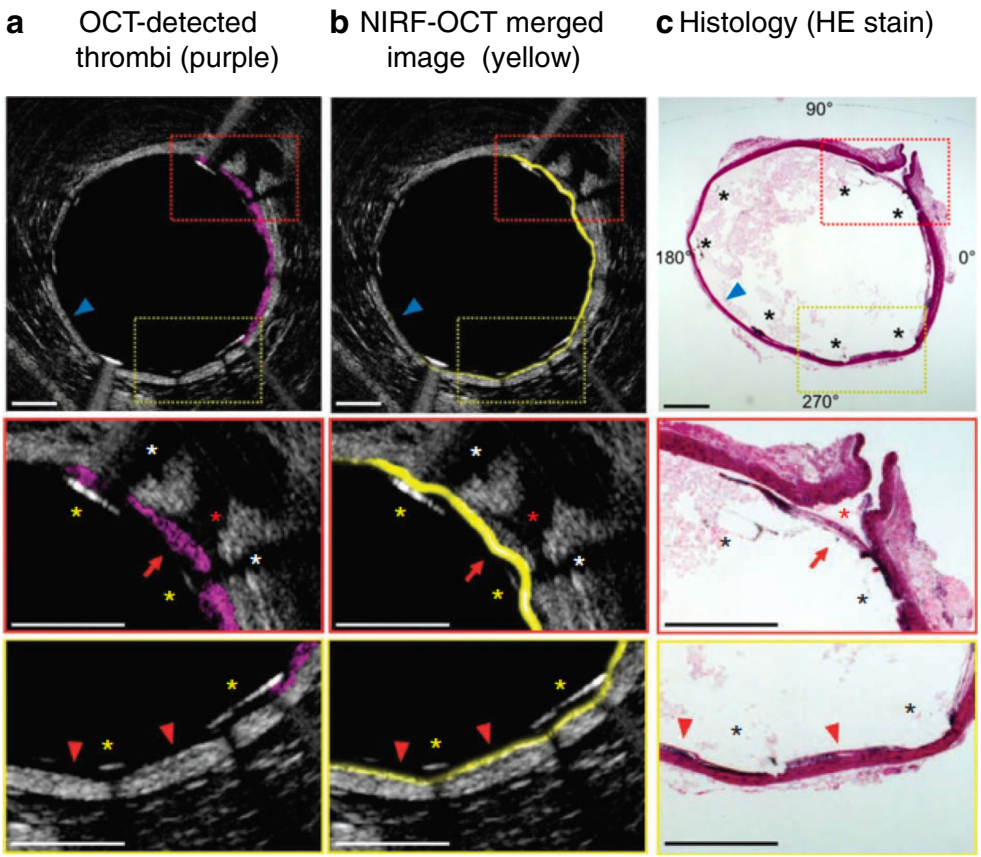

Fig. 3 Integrated NIRF-OCT molecular-microstructural imaging. In vivo NIRF-OCT imaging of a Cy7-labeled fibrin-coated stent implanted in a rabbit iliac artery. NIRF signal (*yellow*, **b**) is evident at legions where thrombi was detected by OCT and histology (*red arrow in middle right panel*), while the NIRF signal was negligible where OCT and histology did not show evidence of thrombi (*blue arrow*, *upper right panel*). In the lower right histology panel, the *red arrowhead* indicates the region where NIRF and histology showed evidence of thrombi, whereas stand-alone OCT (*lower left panel*) could not resolve this thin layer of fibrin. *Scale bar* = 500 um. Modified by permission from Nature Publishing Group/Macmillan Publishers Ltd. from Reference [7], Yoo H, Kim JW, Shishkov M et al. Intra-arterial catheter for simultaneous microstructural and molecular imaging in vivo. Nat Med 2011;17:1680–4

NIRF-IVUS Imaging

A new combined imaging system utilizing NIRF and intravascular ultrasound (IVUS) is under development. While OCT provides excellent high-resolution intravascular images, OCT has limited ability to image in deep tissue, precluding atheroma area measurements such as plaque burden. Another limitation of OCT is the requirement of the displacement of the blood by saline to enable imaging of the arterial wall. At present, IVUS is currently the predominant intracoronary imaging modality [8, 9], and it offers the capability of imaging in deeper tissue and does not require flushing while pullback. Therefore, the availability of NIRF-IVUS system will further accelerate

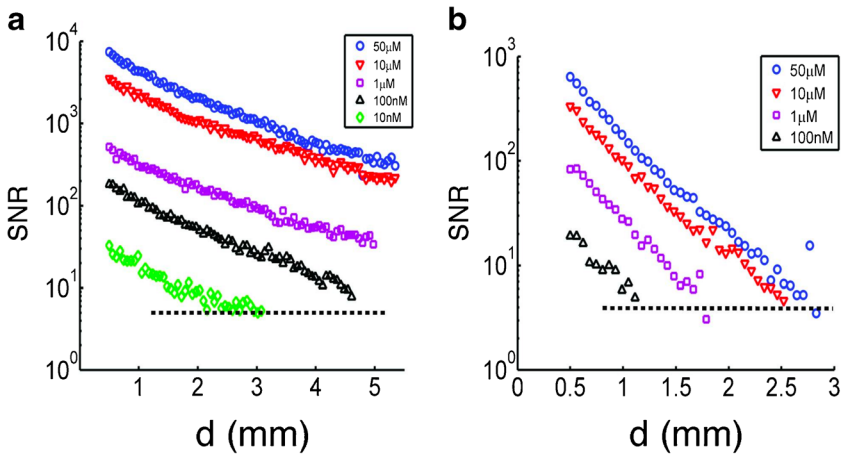

Fig. 4 Attenuation of NIRF signal by distance in saline and in blood-like phantom solutions. The signal-to-noise ratio (SNR) was measured for various NIRF target concentrations at various distances through (**a**) saline and in (**b**) blood-like solution, respectively. *Dashed line* indicates the sensitivity limit of the system. Greater NIRF signal attenuation was present in blood-like liquid compared to saline. Modified by permission from Elsevier from Reference [6], Jaffer FA, Calfon MA, Rosenthal A et al. Two-dimensional intravascular near-infrared fluorescence molecular imaging of inflammation in atherosclerosis and stent-induced vascular injury. J Am Coll Cardiol 2011;57:2516–26. Permission conveyed through Copyright Clearance Center, Inc

intracoronary NIRF molecular imaging, although sensitivity through blood and distance correction through blood will need to be addressed.

Advances in Post-Processing of NIRF-OCT Data

Development of combined NIRF and structural imaging such as OCT and IVUS allows quantification of NIRF signals and comparison by distance compensation. As the NIRF signal is dramatically attenuated by distance in blood and even in saline (Fig. 4), measuring the distance between vessel wall and catheter and NIRF signal compensation based on that distance is critically important for the quantification.

To measure the distance between the catheter and wall, it was previously required to manually trace the luminal border of the vessel of every axial slide to generate distance-compensated NIRF images. To minimize this time-consuming manual effort, we have developed an automated distance compensation algorithm [10•], allowing to process an entire pullback of 200 axial slices within 8.8 s, without manual tracing. This automatic processing algorithm also demonstrated excellent accuracy (similarity coefficient = 0.97 ± 0.33) and rapid, automated visualization of dual modality of NIRF-OCT images for the quantification of NIRF signal in the atherosclerotic plaque.

Application of Intravascular NIRF Imaging to Atherosclerotic Disease

Development of intravascular NIRF imaging catheters has been successfully achieved and tested in several preclinical models [5, 6]. In addition to catheter systems, NIRF molecular imaging requires injectable NIRF molecular/biological imaging agents to target and illuminate specific molecules. There are several NIRF imaging agents to illuminate important biological features of atherosclerotic disease, including several that are translatable for human investigation.

NIRF Imaging of Inflammatory Cysteine Protease Activity

Inflammation in the atherosclerotic plaque is an important characteristic of high-risk plaques. Inflammatory cytokines induced from foam cells promotes the disruption of fibrous cap, exposing thrombogenic molecules to circulating blood in coronary artery [11].

To image inflammatory activity in atheroma, a protease-activatable NIRF imaging agent was designed [12–14], termed Prosense/VM110. After the intravenous injection of Prosense/VM110, the NIRF probe circulates in the blood in the quenched state without NIRF signal. Cleavage of lysine-lysine bonds by active enzymes liberates previously quenched fluorophores, resulting in an amplified NIRF signal within atheroma (Fig. 5).

Prosense/VM110 has been used in rabbit atherosclerosis model and imaged by first-second generation stand-alone NIRF imaging catheter and NIRF-OCT system [5–7]. Prosense/VM110 can also illuminate coronary stent-induced inflammation [6], and can provide new insights into the development of stent restenosis [15].

NIRF Imaging of Fibrin Deposition to Monitor Stent Healing

Sustained fibrin deposition, uncovered struts, and inflammatory cell infiltration are established risk factors for future stent thrombosis [16, 17]. Therefore, visualizing fibrin deposition by molecular imaging technique simultaneously assessing strut coverage by OCT is a promising approach to identify stent thrombus-prone coronary stents in vivo.

The ability of NIRF-OCT catheter to identify micro-thrombus was initially demonstrated by imaging a Cy7-labeled fibrin-coated stents. Cy7-labeled fibrin-coated stents were implanted in cadaveric human coronary artery and in a living rabbit iliac artery. NIRF-OCT identified micro-thrombus beyond the detection level by stand-alone OCT [7]. However, this approach required preincubation of a stent with already NIR fluorophore-labeled fibrin, which is not clinically applicable.

To test the ability of NIRF-OCT to illuminate endogenous micro-fibrin deposition at coronary stents in a translatable manner, a new injectable fibrin-targeted molecular imaging agent was developed, named FTP11-Cy7 [18]. FTP11-Cy7 was designed based on the clinically tested fibrin-targeted MRI agent, EP-2104R [19–22], allowing future clinical translation. After in vivo testing of the agent in mice DVT model demonstrated fibrin specificity [18], we have recently applied FTP11-CyAm7 (CyAm7 = NIR fluorophore) to imaging micro-fibrin deposition at coronary stents in vivo [23•]. Molecular imaging with OCT provided high-resolution structural imaging that enabled the accurate mapping of fibrin deposition along with the stent struts (Fig. 6). Importantly, a detailed study of BMS and DES demonstrated that OCT stent coverage, typically a surrogate for a healed stent, did not always represent healthy tissue coverage. In DES stent edges in the rabbit at 1 month post implantation, it was found that up to 20 % of OCT-covered stents were actually covered by NIRF-detected fibrin, indicating an *unhealed*, rather than a healed stent. This observation may have clinical implications for standalone OCT studies investigating stent coverage as a surrogate for stent healing.

Clinical Application: NIRF Imaging of Inflamed, Lipid-Rich Atheroma

Prosense/VM110 is a promising molecular imaging agent to illuminate inflammatory activity in vivo; however, its

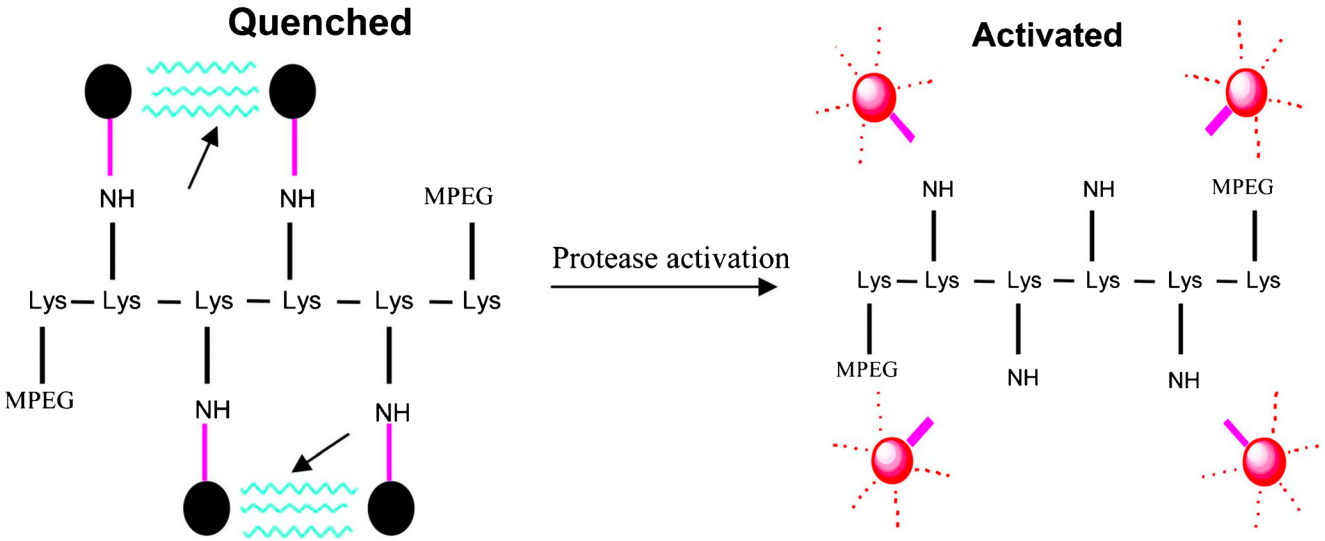

Fig. 5 Schematic mechanism of NIRF signal activation for a lysine-cleavable protease activatable agent (Prosense/VM110). The NIRF signal of Prosense/VM110 is self-quenched without cleavage at the enzyme recognition sites (*arrow*), allowing low NIRF signal in the circulating blood. After the cleavage by the enzymatic activity, strong NIRF signal can be detected at the inflamed tissue. Reproduced by permission Elsevier from reference [12], Shah K, Weissleder R. Molecular optical imaging: applications leading to the development of present day therapeutics. NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics 2005;2:215–25. Permission conveyed through Copyright Clearance Center, Inc

application for human use is not yet available. We recently identified indocyanine green (ICG) as a repurposable NIRF molecular imaging agent to visualize lipid-laden, inflamed atherosclerotic plaque [24]. ICG has been used clinically for decades to assess liver or cardiac function, or to perform retinal angiography in the clinic. Therefore, its safety in clinical use is already established and widely known. ICG is a promising new imaging agent to accelerate our understanding of biological features of coronary atherosclerotic plaque in human. A recent study showed that intravascular NIRF-OCT imaging can detect ICG-illuminated coronary plaque in swine in vivo [25]. Further work to understand whether ICG can

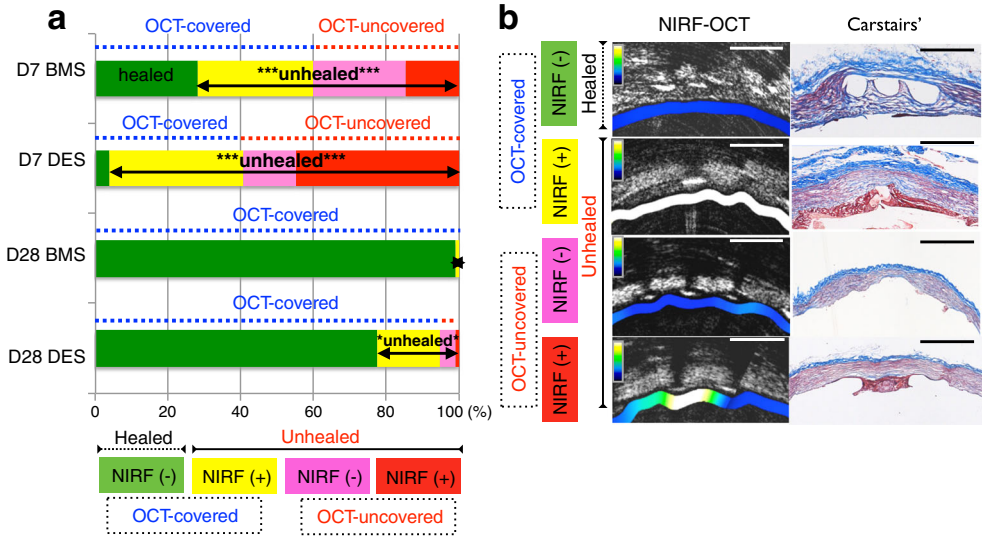

Fig. 6 In vivo NIRF-OCT imaging of fibrin deposition to characterize stent healing on a molecular and microstructural level. **a** Fibrin molecular NIRF-OCT imaging assessment of the healing status of edge stent struts, by stent age (day 7 or 28), and by stent type (bare metal stent, BMS or drug-eluting stent, DES). At day 7, approximately 60 % of BMS struts and 40 % of DES struts were identified as OCT-covered (*green + yellow* groups), however, most of covered struts in DES were actually NIRF-fibrin positive. At day 28, approximately 20 % of OCT-*covered* day 28 DES struts still remained NIRF-fibrin positive. **b** Representative NIRF-OCT and matched Carstairs' fibrin staining. Reproduced by permission from Oxford University Press from reference [23•], Hara T, Ughi GJ, McCarthy JR et al. Intravascular fibrin molecular imaging improves the detection of unhealed stents assessed by optical coherence tomography in vivo. Eur Heart J 2015;in press

target aspects of human atheroma were also recently reported in a carotid endarterectomy clinical trial [26]. These results suggest ICG can target human carotid atheroma exhibiting endothelial abnormalities, and thus ICG may help accelerate first-in-human intravascular NIRF studies.

Clinical Applications: Human Intracoronary NIR Autofluorescence (NIRAF)-OCT Imaging

A first-in-human evaluation of a intracoronary NIRF-OCT has been recently completed [27]. This clinical study employed a NIRF-OCT system to detect NIRF autofluorescence (NIRAF) from coronary atheroma, without the injection of a NIRF imaging agent such as ICG. Previous ex vivo data revealed increased NIRF autofluorescence from the necrotic cores of coronary atheroma in cadaveric subjects [28], indicating NIRAF-OCT imaging might provide additional biological information beyond OCT-based structural imaging. After receiving an investigation device exemption (IDE) from the FDA, we performed a clinical trial NIRAF-OCT imaging in 12 human patients with coronary artery disease. NIRAF-OCT imaging was successful in all patients and completed without adverse events. Interestingly, increased NIRAF was evident in a high-risk morphologic coronary plaques such as OCT fibroatheroma, plaque rupture, and fibroatheroma associated with in-stent restenosis. The overall data support that NIRAF-OCT is a safe and informative imaging strategy to characterize coronary plaque features. In addition, this study provides a foundation for targeted NIRF imaging using adjunctive molecular imaging agents.

Conclusions

Intravascular NIRF molecular-structural imaging is a promising high-resolution translatable approach to enable molecular and biological imaging in human coronary arteries. Illuminating key biological features simultaneously with the structural imaging via OCT or IVUS will accelerate the understanding of pathological mechanisms underlying the progression of coronary atherosclerotic disease.

Both NIRF imaging systems and NIRF imaging agents show considerable translational potential. A recently completed first-in-human NIRAF-OCT study now provides a foundation for targeted NIRF-OCT molecular imaging in the cardiac catheterization laboratory. From a NIRF imaging agent standpoint, ICG is available for testing, and newer clinical agents such as angiogenesis-targeted agents (e.g. bevazicumab, https://clinicaltrials.gov/ct2/show/NCT01972373) may soon be clinically available for atheroma assessment.

In conclusion, the recent progress of intravascular NIRF molecular imaging technology towards clinical use offers substantial potential to better understand the pathobiology of coronary artery disease or coronary stent failure, and to help identify better high-risk patients vulnerable to acute myocardial infarction and sudden cardiac death.

Compliance With Ethical Standards

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Conflict of Interest TH reports no conflicts of interest. FAJ reports personal fees from Abbott vascular, personal fees from Boston Scientific, grants from Kowa, grants from Siemens, grants from Canon, outside the submitted work; in addition, FAJ has a patent pending related to intravascular NIRF imaging.

Human and Animal Rights and Informed Consent With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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