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특집 : NIR Fluorescence Imaging Systems 및 Optical Packaging

NIR Fluorescence Imaging Systems with Optical Packaging Technology

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Abstract: Bioimaging has advanced the field of nanomedicine, drug delivery, and tissue engineering by directly visualizing the dynamic mechanism of diagnostic agents or therapeutic drugs in the body. In particular, wide-field, planar, near-infrared (NIR) fluorescence imaging has the potential to revolutionize human surgery by providing real-time image guidance to surgeons for target tissues to be resected and vital tissues to be preserved. In this review, we introduce the principles of NIR fluorescence imaging and analyze currently available NIR fluorescence imaging systems with special focus on optical source and packaging. We also introduce the evolution of the FLARE intraoperative imaging technology as an example for image-guided surgery.

Keywords: NIR fluorescence, Optical imaging, Intraoperative imaging, Image-guided surgery, Optical packaging

1. Introduction

Bioimaging is a promising field of research that utilizes optical fluorescence light to see, and ultimately facilitate otherwise sophisticated surgical procedures. Current other diagnostic imaging modalities used routinely in patient care are: x-rays (plain film and fluoroscopy), computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), single-photon emission computed tomography (SPECT), and positron emission tomography (PET).[1)] Although x-ray fluoroscopy and US are frequently used for image-guided surgery in the clinic, the rest of imaging modalities are mostly limited to being capable of preoperative diagnostic measurements.

The unmet clinical need in surgery stems from the fact that there are currently no clinically available real-time intraoperative imaging systems that guide surgeons to find target tissues and to avoid vital tissues. For example, with modern surgical techniques, 20-25% of breast cancers are still being resected incompletely[2,3)] and local recurrence remains unsatisfactorily high about 12-28%.[4)] Moreover, nerve damage during many types of surgery, resulting in post-surgical neuralgia and loss of function, occurs in 20,000 to 600,000 patients per year in the U.S. alone.[5)] Being able to see structures that need to be resected, such as malignant cancerous tissue, and structures that need to be avoided, such as blood vessels and nerves, is a profound unmet clinical need. In this review, we discuss currently available NIR fluorescence imaging systems with special focus on optical sources and their packaging technology.

2. NIR Fluorescence Imaging Systems

2.1. NIR Window

Unlike visible light, which cannot penetrate into blood and tissue more than a few hundred microns due to high photon attenuation from absorbance and scatter, the near-infrared window (NIR Window) is the optical window utilizing NIR fluorescence light which has the range of emission wavelength between 650 nm to 900 nm.[6)] It is well known that absorption and scatter properties greatly affect the photon penetration into living tissue. Because of low absorption and scattering as well as extremely low autofluorescence in the NIR window, *in vivo* optical imaging using the NIR fluorescence light could be improved significantly (Fig. 1).

Autofluorescence is natural emission of endogenous fluorophores in the body, which appears when tissue absorbs fluorescence light.[7)] Tissue autofluorescence can

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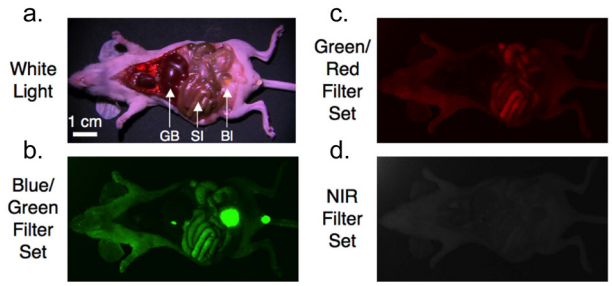


Fig. 1. Endogenous tissue autofluorescence imaging depending on filter sets and excitation fluorescence light. (a) Color image of a hairless, athymic nu/nu mouse. Tissue autofluorescence was imaged using 3 different excitation/emission filter sets: (b) blue/green (460–500 nm/505–560 nm); (c) green/red (525–555 nm/590–650 nm); and (d) NIR (725–775 nm/790–830 nm). The fluence rate provided by each filter set was adjusted to 2 mW/cm^2. Arrows mark the location of the gallbladder (GB), small intestine (SI) and bladder (Bl). [Adapted from Frangioni, JV.[7] Copyright permission from Elsevier].

severely affect signal-to-background ratio (SBR), which is the basic principle of intraoperative imaging. Using the NIR window, the problem of autofluorescence can be essentially eliminated in bioimaging. Figure 1 shows the wavelength-dependent autofluorescence of tissues and organs in an athymic nude mouse.[7] 'Green' autofluorescence of the skin and viscera, gallbladder, small intestine, and bladder is all relatively high when the whole body is excited with the blue light. When 'red' filter set is used, the autofluorescence of gallbladder and bladder is noticeably decreased while intestinal signals still remains significantly under the green light. However, the use of NIR fluorescence light eliminates such autofluorescence in most tissues significantly, resulting in reduced background signal and improved SBR.

2.2. Real-Time Intraoperative Imaging Systems

2.2.1. Fluorescence excitation light sources

There are 3 major technologies capable of producing fluorescence light for excitation of exogenously injected NIR fluorophores: filtered-broadband sources, light-emitting diodes (LEDs), and laser diodes (LDs).

Filtered-Broadband Sources: There are various broadband light sources based on optical semiconductors, e.g. superluminescent diodes. They typically exhibit a high spatial coherence, making it easy to focus the output tightly or to deliver it through an optical fiber, even a single-mode fiber; therefore mostly used for the light source of absorption spectroscopy. The major problem applying this broadband source for optical imaging system is efficiency. Most of the photons produced by the source are discarded in order to filter excitation light to narrow the target band, and in most cases excessive heat is generated. These broadband sources also have a relatively large solid angle, that is, only a small fraction of the optical power propagates towards the surgical field.[8] Concentrating optical power inside light guides using mirrors and lenses is also difficult. Because of these issues, there are few applications in image-guided surgery where broadband sources would be optimal. Furthermore, it is often difficult to focus such filtered-broadband light on a desired field of view (FOV) at a long working distance.[9,10]

Light-Emitting Diodes (LEDs): LEDs are an efficient light source for fluorescence imaging because of their efficient conversion of electrical energy into optical energy, high power, spectral confinement, and cost. Typically the full-width at half maximum (FWHM) is less than 50 nm and the power densities up to 300 W/cm^2.[11] Working with LEDs for surgical imaging, however, can be challenging, mostly because of temperature concerns, wiser bandwidths, and difficulty in assembling large arrays.[12] For example, heat dissipation is a major challenge for dense arrays. Therefore, excitation filters and collimators as well as lensing (either inherent to epoxy LEDs or external) are required to reduce the spectral FWHM and to concentrate optical power within the FOV.

Laser Diodes (LDs): LDs are the most confined spatially and spectrally, but expensive at high power. They can be difficult to integrate, can trigger safety concerns related to maximal permitted exposure (MPE), and require the use of personal protective equipment such as laser goggles. LDs also require precise control in current and temperature using a proportional-integral-derivative feedback control loop as temperature variations induce changes in wavelength. High temperatures reduce the lifetime of the diode significantly. Recently, NIR diodes in the 1-2 W range have become available, although not every wavelength is available in high power packages. In some situations, a major problem with coherent sources like LDs is speckle, which may have to be removed prior to illuminating the surgical field by either rotating a diffuser or vibrating a fiber at frequencies much higher (typically 10-times) the camera frame rate.[9,10,12]

2.2.2. Commercially available NIR imaging systems

Most *in vivo* imaging systems currently available are developed in 3 major categories depending on the application purposes: 1) closed chamber type, 2) handheld type, and 3) open air type imaging systems.

1) FMT Series (Perkin Elmer, Waltham, MA, USA): The FMT system is an LD-based tomographic NIR imaging system for small animal imaging. It is available up to 4 channels, capable of utilizing fluorescence wavelength ranging 650-805 nm in a closed housing. Animal imaging cassette is used to capture 3D tomographic, 2D reflectance images. It is also possible to co-register MR, CT, SPECT, and PET scan images with the FMT image.

2) IVIS Spectrum (Perkin Elmer, Waltham, MA, USA): The IVIS spectrum is an LED-based pre-clinical *in vivo* imaging system. It is used for fluorescence imaging spanning 430-850 nm as well as bioluminescence imaging in a closed chamber. It also supports spectral unmixing and automatic co-registration of CT/MRI images on a 3D image.

3) Fluobeam (Fluoptics, France): Fluobeam and Fluostick are handheld LD-based imaging systems used for visualization of circulatory and lymphatic flow during surgical operation. The preclinical version of Fluobeam utilizes NIR fluorescent probes for real-time visual assessment of tumor margin. This system is designed as two separate models with different NIR excitation/emission capabilities: Fluobeam 700 and Fluobeam 800 with excitation 680 nm and 780 nm, emission collection > 700 nm and > 820 nm, respectively.

4) Photodynamic Eye (PDE) (Hamamatsu Photonics, Tokyo, Japan): The PDE system is designed for real-time intraoperative fluorescence imaging ranged from visible to NIR light. It is a portable handheld device with great mobility, and has shown to be effective in sentinel lymph node (SLN) mapping, visualizing blood perfusion, visceral surgery, and burn depth evaluation.

5) Artemis (Quest Medical Imaging, Middenmeer, The Netherlands): The Artemis is an LD-based portable imaging system compatible with fluorescence between wavelength of 400-1000 nm. It is equipped with handheld camera, which could be fixed to movable articulating arms or used as laparoscope for real-time intraoperative imaging. Captured color and NIR fluorescence images are displayed on a screen along with the merged image. Its primary uses are similar to those of PDE.

6) SPY Elite (Novadaq, Richmond, Canada): The SPY Elite is an LD-based NIR fluorescence imaging system used for open air intraoperative imaging. It captures and views fluorescence images for the real-time visual assessment and evaluation of tissue perfusion, and other circulatory abnormalities. This system is already approved by the U.S. FDA for intraoperative surgery including coronary artery bypass grafting, plastic and reconstructive surgeries, and organ transplant.

Fig. 2. Commercially available NIR fluorescence imaging systems. Shown are representative images for 1) FMT (Perkin Elmer), 2) IVIS (Perkin Elmer), 3) Fluobeam (Fluoptics), 4) PDE (Hamamatsu), 5) Artermis (Quest Medical Imaging), 6) Spy Elite (Novadaq), and 7) Solaris (Perkin Elmer).

7) Solaris (Perkin Elmer, Waltham, MA, USA): The Solaris system is designed for open air *in vivo* imaging based on 4 different wavelengths LEDs (470, 660, 750, and 800 nm), of which fluorescence compatible with various imaging probes. The application of Solaris is primarily focused on preclinical therapeutic development and surgical researches.

2.3. FLARE Imaging Systems

Over the past decade, the Center for Molecular Imaging at BIDMC has developed a series of real-time intraoperative imaging systems, named Fluorescence-Assisted Resection and Exploration (FLARE) (Fig. 3). These systems are designed for open air *in vivo* imaging and largely composed of CCD cameras, computer, monitors, and light source (LD or LED). As shown in Figure 4, the FLARE has 3 different light sources and their counterpart cameras: white light for a color video, 700 nm channel, and 800 nm channel. After an exogenous fluorophore is injected, 3 different light sources excite the fluorophore while the cameras capture the emission signals and computer processes and displays real-time image of surgical area on the monitor.

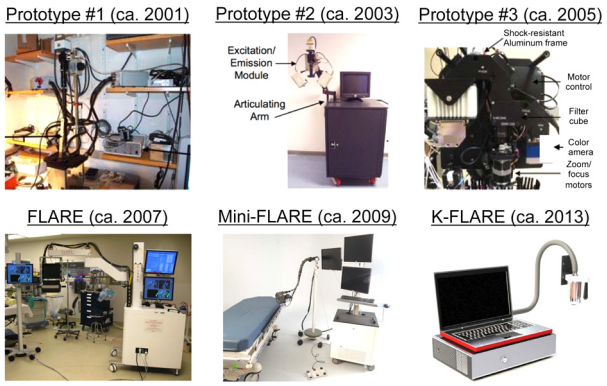


Fig. 3. Historical evolution of the FLARE real-time intraoperative imaging systems developed by the Center for Molecular Imaging at BIDMC from 2001 to 2013.

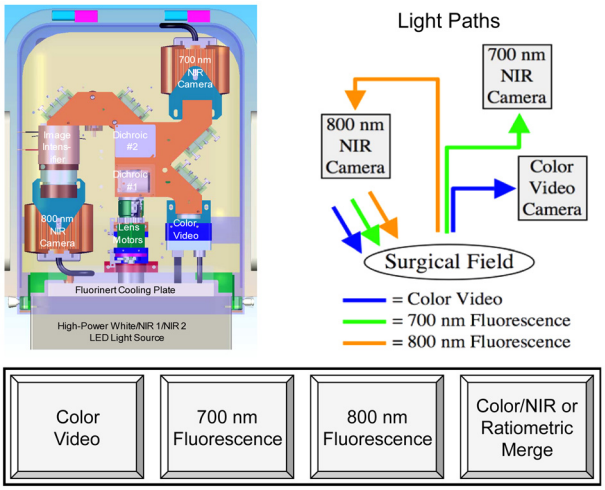


Fig. 4. Detailed schematic drawing of the FLARE imaging head, optical light paths, and filtration. The FLARE imaging system is composed of a color video camera, and two independent and simultaneous NIR cameras (680 nm dichroic mirror/700 nm emission; 770 nm dichroic mirror/ 800 nm emission).

2.3.1. LED-based FLARE systems

The initial version of FLARE imaging systems was built based on compact, heat-dissipating LED modules for real-time intraoperative image-guided surgery.[9,13] Briefly, wavelength-isolated white light (400-650 nm), NIR channel #1 excitation (660-685 nm), and NIR channel #2 excitation (760-790 nm) illuminate up to 15 cm of surgical field, and a 3-CCD camera system with custom filters simultaneously acquires color video and two independent channels of NIR emission centered at 700 nm for NIR channel #1 and 800 nm for NIR channel #2 (Fig. 4).

The LED-based FLARE imaging system was reported previously in detail.[9,13] Briefly, as shown in Figure 5, the imaging head is comprised of a high-power, computer-controlled LED light housing, custom optics and filtration,

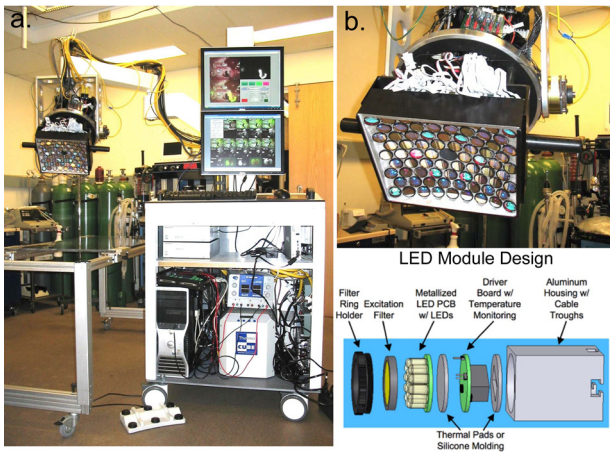


Fig. 5. Overview of an LED-based FLARE imaging system (a) and the design of LED light housing (b) with compact, heat-dissipating modules.

and cameras,[12] and the hardware was engineered to meet all relevant subsections of the AAMI/IEC standard #60601. The system has adjustable FOV from 2.2-15 cm, a resolution of 125-625 μm, and an 18" working distance between the imaging head and the patient with fluence rates of 4 mW/cm^2 and 14 mW/cm^2 for 670 nm and 775 nm excitation light, respectively.[13] 40,000 lux white light (400-650 nm) was also used to illuminate the surgical field during operation.[13]

The major challenge of the use of densely packed LEDs is heat generation over time. To eliminate this issue, 5 mm epoxy LEDs were arranged in a trigonal pattern with 3 central and 9 peripheral positions on a printed circuit board (PCB) with a minimal solder mask around each lead hole.[12] Moreover, to eliminate heat, tens of additional holes were drilled in the PCB heat on a metallized board, and anodized aluminum housing was used with the secondary 400 W cooling plate. Finally, the housing was continuously water-cooled by running a 400 W Thermocube (Solid State Cooling, Pleasant Valley, NY) set to 18°C connected to a custom cooling plate (Lauzon Manufacturing, Bennington, VT).[13]

2.3.2. LD-based FLARE systems

Recently, we developed a potable K-FLARE imaging system based on a custom NIR laser light source with commercial grade objective lens and dual sensor camera. Briefly, 660 nm and 760 nm NIR LD sources were packaged onto a single, small footprint board with their cooling elements (see details in Section 3.2). The K-Flare imaging system can be classified as a Class 3R laser device with the 660 nm driven at maximum current and the 760 nm diode operated at 96% of its maximum output. It should be noted that the implementation of illumination setup in

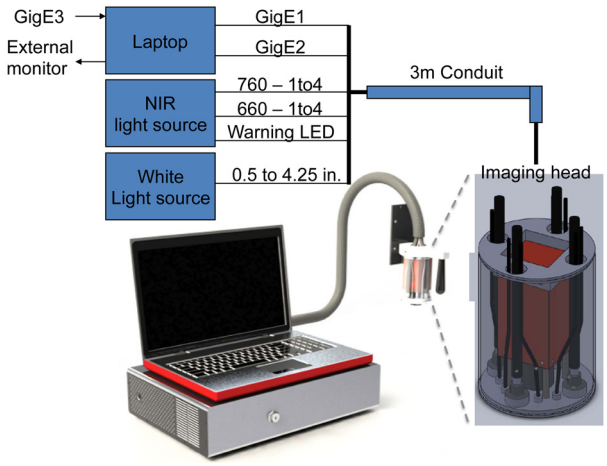
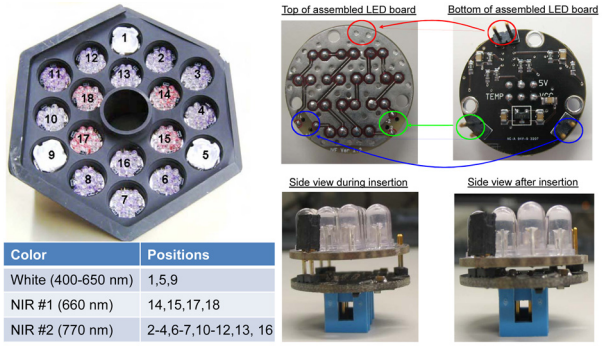


Fig. 6. Laser-based miniaturized K-FLARE imaging system. The K-FLARE system provides simultaneous color video (512×512 pixels), choice of either 700 nm or 800 nm fluorescence, and merge of color video and NIR fluorescence. The fluence rates for 660 nm and 760 nm lasers are 1.0 mW/cm^2 and 3.6 mW/cm^2, respectively, at 13" working distance. 5,500 lux of white light (400-650 nm) is provided to cover FOV of 5.5" during surgery.



Color	Positions
White (400-650 nm)	1,5,9
NIR #1 (660 nm)	14,15,17,18
NIR #2 (770 nm)	2-4,6-7,10-12,13, 16

Fig. 7. Design of light housing and packaging of individual LEDs. Special attention paid to insert the assembled driver board three 2-pin headers into the appropriate holes on the assembled LED Board.

practical settings could be susceptible to multiple losses due to laser filtration, fiber injection and attenuation during transmission. A more reasonable estimate of operating efficiency for both diodes is in the 50-60% range and under these conditions the device provides a maximum fluence of ~1 mW/cm^2 at 660 nm and ~7 mW/cm^2 at 760 nm excitation. The NIR fluorescence contains the following acquisition parameters: exposure, gain, and BCG (brightness, contrast, and gamma) settings.

3. Design of Optical Imaging Systems with Packaging

3.1. Light Housing Design and LED Packaging

For the LED-based mini-FLARE imaging system, individual LED modules were mounted in a small aluminum housing (Fig. 7).[12] MATLAB-based software was used to maximize the packing of light sources with a high fluence rate and multiple wavelengths, which requires input of light element (i.e., LED modules) characteristics, light element size, minimum inter-module spacing, desired working distance, and the central lens hole diameter. To optimize the compactness, we packed as many modules as possible around the central lens hole and modulated the inter-module distances.[9,13] The LED module centers were then projected onto the spherical cap surface. To assemble LED modules efficiently, LED and PCB boards were mated, potted with thermally conductive silicone, and then covered with a color-coded smooth silicone (Albright Technologies, Leominster, MA).[12] Optical packaging is another challenge because of difficulty in lensing that relays white and NIR fluorescent emission light to the cameras, of which considering factors are transmission of light, depth of field, working distance, and FOV to minimize distortion, vignetting, and parfocality. The total optical power from the assembled LED modules ranged from 57-77% of maximum at 18" working distance, with sputtered excitation filters providing wavelength selection with high transmission (typically 98%).

3.2. Imaging Head Assembly and LD Packaging

The LD-based portable K-FLARE imaging system is composed of 3 optical fiber assemblies for illumination, namely the 660 nm and 760 nm NIR fibers and a white light fiber bundle. The illumination head shown in Figure 8 comprises of 12 illumination ports: 4× White Light (LED), 4× 660 nm lasers and 4× 760 nm lasers. Two laser diode modules (one for 660 nm and 760 nm each) were housed in a separate enclosure and were connected to the illumination head via quadfurcated fiber optic bundles with 1 mm core diameter. The maximum output of the 660 nm and 760 nm modules is 1 W and 2.5 W, respectively.

The optical fibers allow uniform distribution of laser/white light via 4 output legs, of which fiber bundles were arranged in a circular configuration resulting in 12 ports on the luminary for attaching the illumination fibers. The white light fibers design were terminated by a ¼" diameter ferrule and inserted directly into the port.

Figure 8 shows a schematic of the imaging head and cable packaging. For white light (400-650 nm), a custom fiber optic assembly was commissioned with the following input specifications: output of 780 lumens, color temperature of 6000 K, and control input intensity of 4 bit encoders. A ½" bundle diameter was chosen as the largest compatible

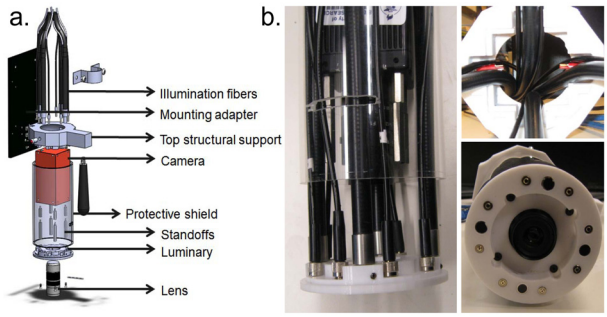


Fig. 8. Components of imaging head assembly (a) and LD packaging (b) with vertical, top, and bottom view of the imaging head. Each face of the camera has 3 fibers (1 white light fiber and 2 fiber legs from each of the NIR fibers). The legs of fibers were arranged in mutually orthogonal directions.

with the LMI-6000 light source, a largest possible area was desired to minimize loss in the coupling between light source and bundle.

Of note, the umbilical cord should be assembled with the package of white light fibers, NIR #1 fibers (660 nm), NIR #2 fibers (760 nm), camera power supply, camera communication cables, and LD supply cables (Fig. 8).

4. Conclusions

In this article, we review the state-of-the art optical fluorescence imaging and various preclinical and clinical NIR imaging systems with the special focus on the optical light source and packaging. The impact of NIR fluorescence imaging systems is enormous in various research fields, especially bioimaging, drug delivery, tissue engineering, and nanomedicine. Since NIR fluorescent light is basically invisible to human eye, specially designed exogenous contrast agents are required to get the NIR fluorescent light within the surgical field to emit photons at the specific locations. When combined with an appropriate NIR fluorophore, these imaging systems enable real-time *in vivo* imaging to highlight the specific structures desired by the surgeon such as pan and sentinel lymph nodes,[14] peripheral nerves,[15] vasculature,[16,17] bone,[18] pancreas,[19] thyroid and parathyroid glands,[20] as well as many tumorous tissues.[6,21-23] The key to future success will be first-in-human trials of new technology, which in turn requires a comprehensive understanding of such design parameters discussed in this article. The next ten years will likely see the explosion or the demise of image-guided surgery using invisible NIR light.

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References

1. J. V. Frangioni, “New technologies for human cancer imaging”, J. Clin. Oncol., 26(24), 4012 (2008).
2. M. R. Bani, M. P. Lux, K. Heusinger, E. Wenkel, A. Magener, R. Schulz-Wendtland, M. W. Beckmann and P. A. Fasching, “Factors correlating with reexcision after breast-conserving therapy”, Eur. J. Surg. Oncol., 35(1), 32 (2008).
3. D. E. Schiller, L. W. Le, B. C. Cho, B. J. Youngson and D. R. McCready, “Factors associated with negative margins of lumpectomy specimen: potential use in selecting patients for intraoperative radiotherapy”, Ann. Surg. Oncol., 15(3), 833 (2008).
4. I. Besana-Ciani and M. J. Greenall, “The importance of margins status after breast conservative surgery and radiotherapy in node positive patients: a follow-up of 10-15 years”, Int. Semin. Surg. Oncol., 5(1), 13 (2008).
5. S. Burke and G. D. Shorten, “When pain after surgery doesn't go away”, Biochem. Soc. Trans., 37(1), 318 (2009).
6. J. H. Lee, G. Park, G. H. Hong, J. Choi and H. S. Choi, “Design considerations for targeted optical contrast agents”, Quant. Imaging. Med. Surg., 2(4), 266 (2012).
7. J. V. Frangioni, “In vivo near-infrared fluorescence imaging”, Curr. Opin. Chem. Biol., 7(5), 626 (2003).
8. A. M. De Grand and J. V. Frangioni, “An operational near-infrared fluorescence imaging system prototype for large animal surgery”, Technol. Cancer. Res. Treat., 2(6), 553 (2003).
9. S. Gioux, H. S. Choi and J. V. Frangioni, “Image-guided surgery using invisible near-infrared light: fundamentals of clinical translation”, Molecular imaging, 9(5), 237 (2010).
10. S. Gioux, V. Kianzad, R. Ciocan, H. S. Choi, C. Nelson, J. Thumm, R. J. Filkins, S. J. Lomnes and J. V. Frangioni, “A low-cost, linear, DC - 35 MHz, high-power LED driver for continuous wave (CW) and fluorescence lifetime imaging (FLIM)”, Proc. Society of Photo-Optical Instrumentation Engineers (SPIE), San Jose, CA, 684807 (2008).
11. N. McAlinden, D. Massoubre, E. Richardson, E. Gu, S. Sakata, M. D. Dawson and K. Mathieson, “Thermal and optical characterization of micro-LED probes for in vivo optogenetic neural stimulation”, Optics letters, 38(6), 992 (2013).
12. S. Gioux, V. Kianzad, R. Ciocan, S. Gupta, R. Oketokoun, J. V. Frangioni. “High-power, computer-controlled, light-emitting diode-based light sources for fluorescence imaging and image-guided surgery”, Molecular imaging, 8(3), 237 (2009).
13. S. L. Troyan, V. Kianzad, S. L. Gibbs-Strauss, S. Gioux, A. Matsui, R. Oketokoun, L. Ngo, A. Khamene, F. Azar and J. V. Frangioni, “The FLARE™, intraoperative near-infrared fluorescence imaging system: a first-in-human clinical trial in breast cancer sentinel lymph node mapping”, Ann. Surg. Oncol., 16(10), 2943 (2009).
14. Y. Ashitate, H. Hyun, S. H. Kim, J. H. Lee, M. Henary, J. V. Frangioni and H. S. Choi, “Simultaneous mapping of pan and sentinel lymph nodes for real-time image-guided sur-

gery", Theranostics., 4(7), 693 (2014).
15. M. H. Park, H. Hyun, Y. Ashitate, H. Wada, G. Park, J. H. Lee, C. Njiojob, M. Henary, J. V. Frangioni and H. S. Choi, "Prototype nerve-specific near-infrared fluorophores", Theranostics, 4(8), 823 (2014).
16. H. S. Choi, K. Nasr, S. Alyabyev, D. Feith, J. H. Lee, S. H. Kim, Y. Ashitate, H. Hyun, G. Patonay, L. Strekowski, M. Henary and J. V. Frangioni, "Synthesis and in vivo fate of zwitterionic near-infrared fluorophores", Angew. Chem. Int. Ed. Engl., 50(28), 6258 (2011).
17. H. Hyun, M. W. Bordo, K. Nasr, D. Feith, J. H. Lee, S. H. Kim, Y. Ashitate, L. A. Moffitt, M. Rosenberg, M. Henary, H. S. Choi and J. V. Frangioni, "cGMP-Compatible preparative scale synthesis of near-infrared fluorophores", Contrast media and molecular imaging., 7(6), 516 (2012).
18. H. Hyun, H. Wada, K. Bao, J. Gravier, Y. Yadav, M. Laramie, M. Henary, J. V. Frangioni and H. S. Choi, "Phosphonated near-infrared fluorophores for biomedical imaging of bone", Angew. Chem. Int. Ed., 126(40), 10844 (2014).
19. H. Wada, H. Hyun, C. Vargas, J. Gravier, G. Park, S. Gioux, J. V. Frangioni, M. Henary and H. S. Choi, "Pancreas-targeted NIR fluorophores for dual-channel image-guided abdominal surgery", Theranostics., 5, 1 (2015).
20. H. S. Choi, S. L. Gibbs, J. H. Lee, S. H. Kim, Y. Ashitate, F. Liu, H Hyun, G. Park, Y. Xie, S. Bae, M. Henary and J. V. Frangioni, "Targeted zwitterionic near-infrared fluorophores for improved optical imaging", Nature biotechnology, 31(2), 148 (2013).
21. M. Hutteman, J. R. van der Vorst, K. N. Gaarenstroom, A. A. Peters, J. S. Mieog, B. E. Schaafsma, C. W. Lowik, J. V. Frangioni, C. J. van de Velde and A. L. Vahrmeijer, "Optimization of near-infrared fluorescent sentinel lymph node mapping for vulvar cancer", Am. J. Obstet. Gynecol., 206(1), 89-e1 (2012).
22. H. S. Choi, W. Liu, F. Liu, K. Nasr, P. Misra, M. G. Bawendi and J. V. Frangioni, "Design considerations for tumour-targeted nanoparticles", Nat. Nanotechnol., 5(1), 42 (2010).

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