



Beth Israel Deaconess
Medical Center



A teaching hospital
of Harvard
Medical School

FLARE™ Technology Portfolio

**Beth Israel Deaconess Medical Center (BIDMC)
Laboratory of Dr. John Frangioni
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Executive Summary: Dr. John Frangioni is pioneering a new surgical imaging technology that combines instrumentation and contrast agents designed to work together.

Its target users are surgeons seeking next generation ability to detect specific tissues. This advantage will translate to better healthcare outcomes by avoiding, for example, follow-up surgeries to excise previously overlooked tumors and accidental injury to nerves or small blood vessels. Human clinical testing is underway and ~27 inventions are available for licensing.

John Frangioni, MD, PhD is Associate Professor in the Departments of Radiology and Medicine at Harvard Medical School, with a joint appointment as Attending Physician and Oncologist in the Department of Hematology and Oncology at BIDMC. John is a leading researcher at BIDMC, a recipient of numerous honors and awards, and author on over 60 papers.

Beth Israel Deaconess Medical Center is a major academic research hospital based in Boston, MA. From its start in 1896, BIDMC has grown to its current stature as a \$212M biomedical research enterprise. BIDMC shares affiliation with Harvard Medical School, the Broad Institute of MIT and Harvard, the Joslin Diabetes Center, and the Dana-Farber/Harvard Cancer Center. For more information, visit www.bidmc.harvard.edu.

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Introduction: *FLuorescence-Assisted Resection and Exploration*, or FLARE™, is a new real time surgical imaging technology. Currently in clinical testing, the FLARE™ system represents a convergent technology that brings together novel imaging instrumentation and consumable contrast agents. By highlighting cancerous tissue in the body, FLARE enables surgeons to easily see and remove diseased tissue while avoiding inadvertent damage to critical structures such as blood vessels and nerves.

FLARE technology was developed by Professor John Frangioni, M.D., Ph.D., of Beth Israel Deaconess Medical Center (BIDMC) and the technology shows particular promise for improving cancer surgery for tumors with boundaries that can be difficult to define, such as breast, prostate, and lung cancers.

The FLARE system is the centerpiece of Dr. Fragnioni's large and growing intellectual property portfolio managed by BIDMC. To help bring this technology to the patient bedside, BIDMC is soliciting interest from corporate partners. Whether through licensing, co-development, or academic exchange, we are interested in any discussion that will nurture the development and commercialization of this technology.

FLARE Science: This medical imaging technology uses near-infrared (NIR) fluorophores. NIR fluorophores are molecular beacons that, when exposed to a specific wavelength of NIR "excitation" light, glow with a NIR fluorescence that is imaged by cameras. Because NIR light is invisible to the human eye, FLARE technology does not disrupt the surgeon's normal visual experience.

Using such NIR contrast agents in conjunction with special cameras allows the surgeon to conduct the procedure with the benefit of a new kind of "NIR sight" and with no visual liability for the standard surgical field.

During a FLARE procedure, images of these "glowing" cancer cells are then superimposed over visible (VIS) light images of the normal surgical field, allowing surgeons to easily see the cancer cells even in a background crowded by blood and other anatomic structures. Software-driven co-registration of VIS and NIR images permits, for the first time, use of NIR fluorescence with visual landmarks necessary for surgeons to navigate their surgical field effectively.

In addition to NIR and VIS light, the system can also image ultraviolet (UV) fluorescence. Since NIR, VIS, and UV imaging all use familiar optical concepts, the FLARE System can be described in general as an "optical imaging" technology.

"NIR sight" with the FLARE optical imaging permits visualization with the extreme sensitivity of fluorescence optics and, by designing NIR fluorophores to target specific tissues, the contrast agents can home in on very specific anatomic features such as tumor metastases or nerves.

Dr. Frangioni compares the system to the old color-by-number paint sets. However, instead of coloring by numbers, the FLARE system will provide surgeons with a means of "cutting by color" with unprecedented sensitivity and specificity.

FLARE™ is a trademark of BIDMC. Use of the term FLARE in commerce in relation to medical imaging is subject to the trademark practices of the U.S. Patent and Trademark Office.

The summer 2008 clinical trials of this technology marked the first time that NIR fluorescence imaging in combination with VIS imaging was used successfully in the clinic.



FLARE Lymph Node Imaging. Improve cancer surgery by revealing hidden anatomic details. Taken during preclinical testing in animals, this photo shows the pseudo-colored trace of lymph flow through the hind leg of a pig. Viewed after injection with NIR contrast agent, the subject was imaged with NIR light by the base FLARE System.

FLARE Instrumentation: Core components of the FLARE system consist of an apparatus combining VIS and NIR cameras and light emitting diode (LED) light sources for NIR fluorescence. The instrumentation integrates a video monitor, computer, and software and is currently being used in operating rooms around the world.

FLARE Contrast Agents. The future of the technology is in the consumable contrast agents that will be used in conjunction with the instrumentation. Teams led by Dr. Frangioni are developing new NIR fluorophore contrast agents and using existing ones with the following attributes:

- 1) Targeting moieties to direct the contrast agent to tissue of interest
- 2) Beacon moieties that may offer—alone or in combination—NIR, VIS, UV, and radioscintigraphic signals for imaging
- 3) Ranges in size from small drug-like molecules to macromolecular complexes
- 4) FDA approval status that is either already established or readily definable

Product Concepts

Different versions of FLARE instrumentation are possible for commercialization:

- I. Base FLARE System: NIR / NIR / VIS
 - First generation system currently in human clinical testing (2008)
 - Used for sentinel lymph node mapping in breast and lung cancer patients
 - See BIDMC 1027 and related Contrast Agent offerings

- II. Portable Second Generation FLARE System: NIR / VIS
 - Prototype stage
 - See BIDMC 1027 and related Contrast Agents

- III. NIR-Nuclear FLARE System: NIR / Radioscintigraphy
 - Currently in development through a licensing partnership
 - See BIDMC 1027 and Contrast Agent offerings including BIDMC 1164

- IV. Trimodal FLARE System: NIR / UV / VIS
 - Early concept stage
 - See BIDMC 1027 and related Contrast Agents

- V. Scope Systems:
 - Utilize the core hardware for the Base, Handheld, or Trimodal FLARE Systems adapted with an appropriately designed endoscope, laparoscope, bronchoscope, or proctoscope component
 - See BIDMC 1027 and other Contrast Agent offerings

- VI. Contrast Agents
 - Different versions of FLARE -ready contrast agents are possible for commercialization
 - Each product opportunity will depend on which FLARE instrument is in use and which medical need is served. As the instrumentation technology grows in clinical adoption, the demand for NIR contrast agents will grow. The contrast agents primed for preclinical and clinical R&D.

Intellectual Property – FLARE Instrumentation

BIDMC 1027: Pending US application
Available for licensing

Claims: Combined use of NIR imaging and novel FDA-approved NIR fluorophore contrast agent

Intellectual Property – Contrast Agents

BIDMC 759: US patent # 7,181,266 B2, others pending
Available for licensing

Claims: Quantum dot contrast agents for NIR imaging of blood vessels and mapping sentinel lymph nodes

Application: cancer

Development status: preclinical studies to be initiated

Note: Jointly owned by BIDMC and MIT

BIDMC 793: Pending US application
Available for licensing

Claims: contrast agent scaffold that enables the combination of tissue targeting and beacon features for NIR imaging; up to four moieties can be combined; for example, a green NIR fluorophore, a red NIR fluorophore, a UV fluorophore, and an antibody targeting a specific kind of tumor; cross-modal ability, with a multimodal FLARE instrument, would permit extreme specificity and sensitivity in surgical tissue imaging

Application: general

BIDMC 815: Pending US patent
Available for licensing

Claims: derivatized albumin NIR contrast agent ideal for locating blood vessels and lymphatic drainage

BIDMC 1033: Two worldwide patent applications pending
Available for licensing

Claims: Modified NIR contrast agent; key attributes include:

- Optimized and tailorable performance in NIR imaging applications
- High aqueous solubility and stability
- Minimized non-specific tissue binding
- Tune-able bio-distribution and clearance properties
- Potential “stealth” properties yield lower immunogenicity
- Ability to be conjugated to tissue targeting moieties
- Used alone or in combination with other tissue targeting moieties for NIR imaging
- Design addresses for regulatory approval process

Application: general NIR imaging

Development status: synthesis underway to permit 2009 preclinical evaluation

BIDMC 1164: Patent application is in preparation

Invention available for licensing

Claims: dual-modality contrast agent sentinel lymph node mapping; builds on the contrast agents for BIDMC 1033 to refine targeting to sentinel lymph node channels for NIR imaging

Application: sentinel lymph node mapping

Development status: ready for synthesis and proof-of-concept

Intellectual Property – Other

BIDMC 880: U.S. Patent #7,288,759

Available for licensing

Claims: Tissue phantoms for training surgeons in use of FLARE

Application: general NIR imaging

Development status: in current use

Representative Publications

Real-time assessment of cardiac perfusion, coronary angiography, and acute intravascular thrombi using dual-channel near-infrared fluorescence imaging.

Tanaka E, Chen FY, Flaumenhaft R, Graham GJ, Laurence RG, Frangioni JV.

J Thorac Cardiovasc Surg. 2009 Jul;138(1):133-40.

The FLARE™ Intraoperative Near-Infrared Fluorescence Imaging System: A First-in-Human Clinical Trial in Breast Cancer Sentinel Lymph Node Mapping. Troyan SL, Kianzad V, Gibbs-Strauss SL, Gioux S, Matsui A, Oketokoun R, Ngo L, Khamene A, Azar F, Frangioni JV. *Annals of Surgical Oncology* 2009 July [page citation pending]

Lymphatic drainage of the peritoneal space: A pattern dependent on bowel lymphatics. Parungo CP, Soybel DI, Colson YL, Kim S-W, Ohnishi S, De Grand AM, Laurence RG, Soltesz EG, Chen FY, Cohn LH, Bawendi MG, Frangioni JV. *Ann Surg Onc.* 2007;14:296-298.

Image-guided oncologic surgery using invisible light: Completed pre-clinical development for sentinel lymph node mapping. Tanaka E, Choi HS, Fujii H, Bawendi MG, Frangioni JV *Ann Surg Onc.* 2006;13:1671-1681.

Tissue-like phantoms for near-infrared fluorescence imaging system assessment and the training of surgeons. De Grand AM, Lomnes SJ, Lee DS, Pietrzykowski M, Ohnishi S, Morgan TG, Gogbashian A, Laurence RG, Frangioni JV *J Biomed Opt.* 2006;11:14007.

Improved optical sub-systems for intraoperative near-infrared fluorescence imaging. Gioux S, De Grand AM, Lee DS, Yazdanfar S, Idoine JD, Lomnes SJ, Frangioni JV. In: Analoui M, Dunn DA, editors. Proceedings of SPIE (International Society for Optical Imaging). Optical Methods in Drug Discovery and Development Volume 6009; 2005; Oct 23-26; Boston, MA. Bellingham, WA; 2005. p. 39-48.

Internet Media Presence

1. <http://www.frangionilab.org/index.html>
2. http://www.rsna.org/Publications/rsnanews/November-2008/innovation_feature.cfm
3. http://w1.siemens.com/innovation/en/publikationen/publications_pof/pof_fall_2008/frueher_kennung/diagnostik.htm