Personalized Medicine vs. Killer Apps in Near-Infrared Fluorescence-Guided Surgery

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Disclosures

- This talk mentions the off-label use of indocyanine green and methylene blue, two NIR fluorophores that are FDA-approved for other indications.
- The FLARE™ imaging system is investigational only and not approved for the indications shown.
- FLARE™ technology is owned by Beth Israel Deaconess Medical Center, a teaching hospital of Harvard Medical School.
- As inventor, Dr. Frangioni receives royalties from Beth Israel Deaconess Medical Center for FLARE™ technology.
- Dr. Frangioni has licensed FLARE™ technology from the Beth Israel Deaconess Medical Center and is CEO of the companies Curadel™, Curadel ResVet Imaging™, and Curadel Surgical Innovations.

Outline

I. Definitions and Scope of the Problem

II. Clinical Translation and Commercialization

III. The Personalized Medicine Perspective

IV. The Killer App Perspective

V. What the Future Might Bring

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The Field of NIR Fluorescence-Guided Surgery

Park or Throttle + Brake

Why NIR Fluorescence for Image-Guided Surgery?

Because of 4 physical principles:

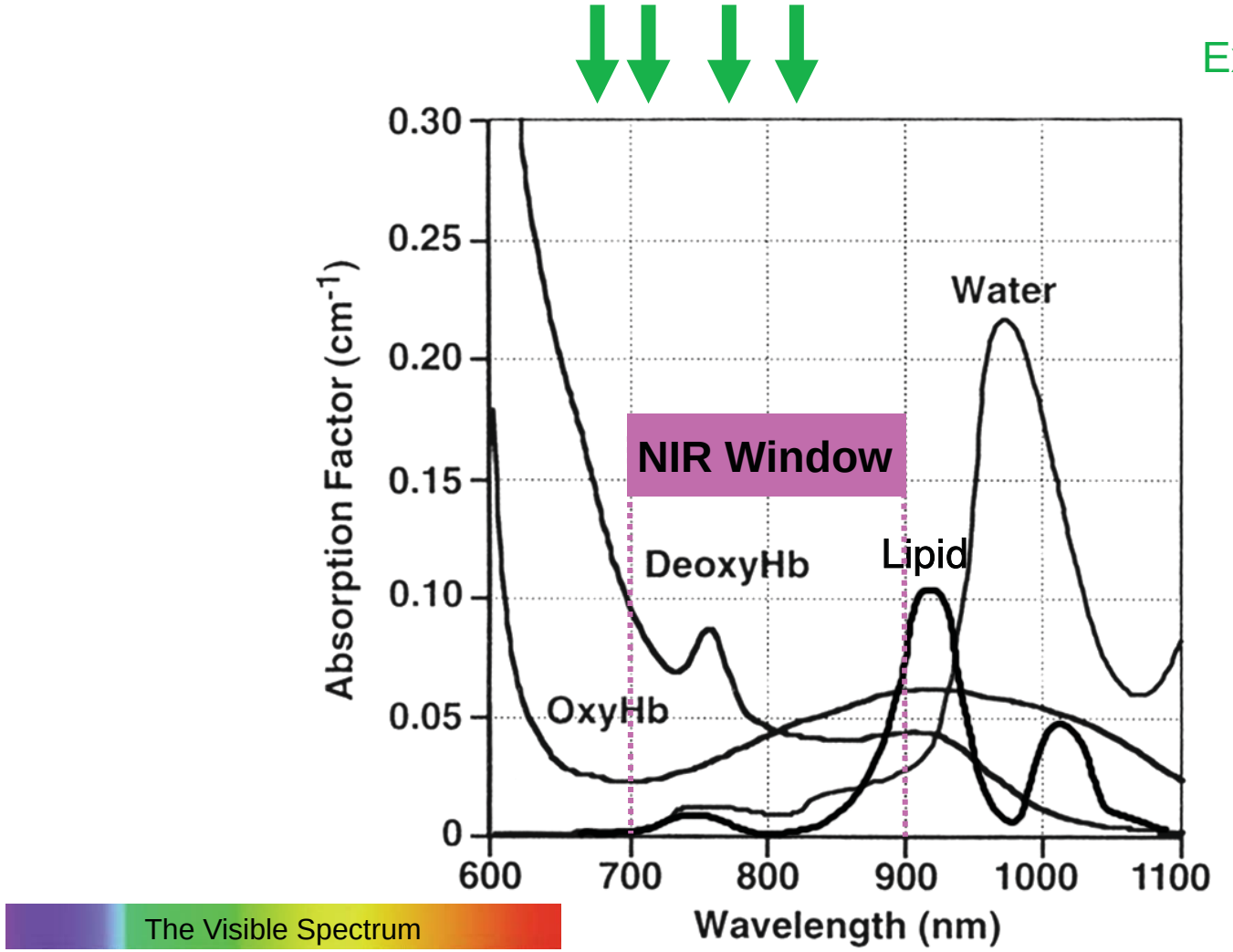
1) Photon absorption is minimal
2) Photon scatter is minimal
3) Autofluorescence is minimal
4) NIR light is invisible to the human eye

Benefits are:

- High contrast: “Bright stars on a black sky”
- No change to the look of the surgical field
- Any object can be potentially be highlighted
- Real-time intraoperative imaging
- Millimeter, instead of micron, depth detection

1) Photon Absorption is Minimal in the NIR

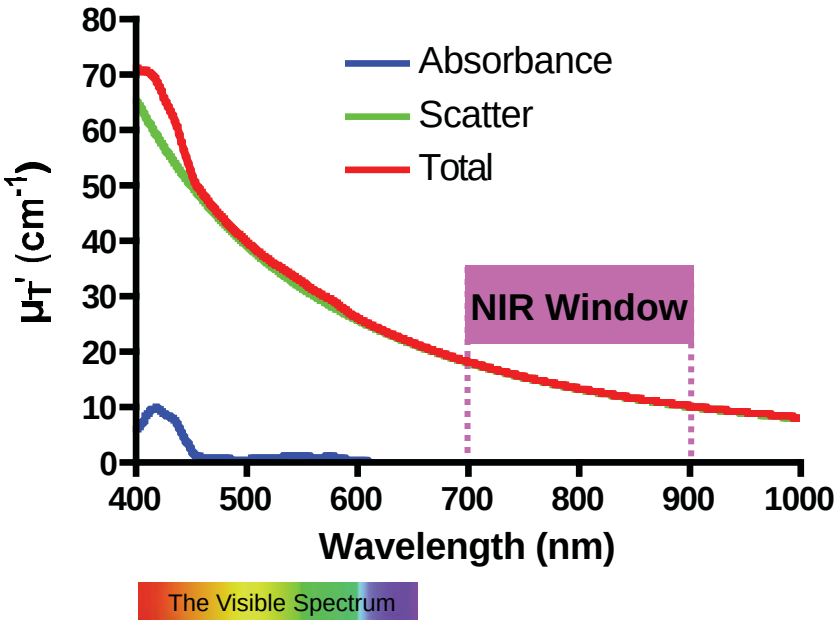
Exogenous Contrast



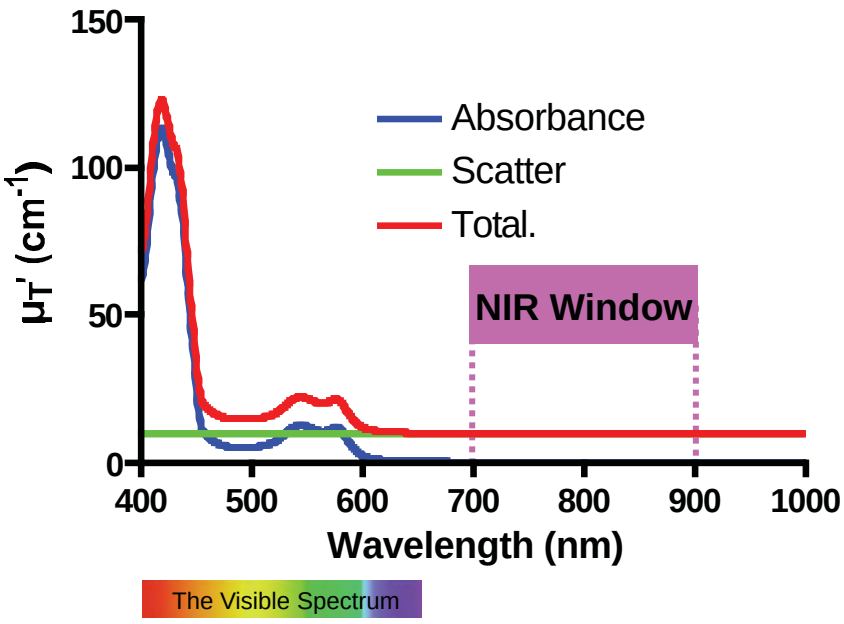
From Chance, Ann N Y Acad Sci, 1998. 838: 29-45, with the addition of lipid data from Conway et al., Am J Clin Nutr, 1984. 40: 1123-30, scaled appropriately

2) Photon Scatter is Minimal in the NIR

Skin (Rayleigh-Type, i.e. Wavelength-Dependent Scatter)

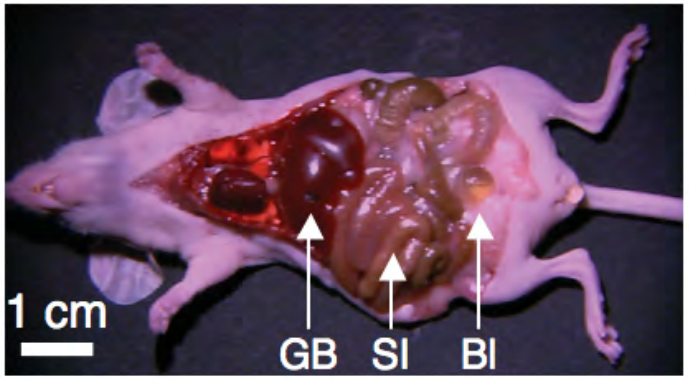


Breast (Mie-Type, i.e., Non-Wavelength-Dependent Scatter)

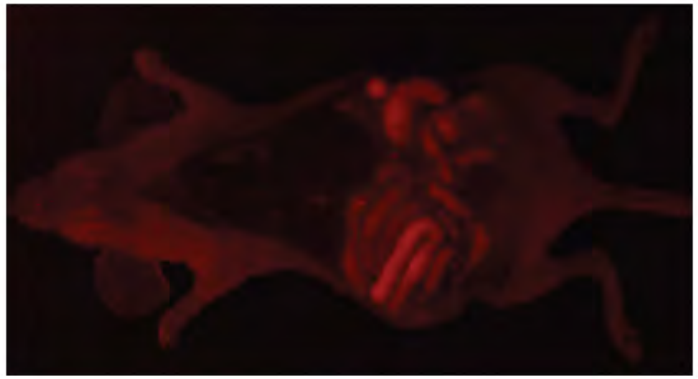


3) Autofluorescence is Minimal in the NIR

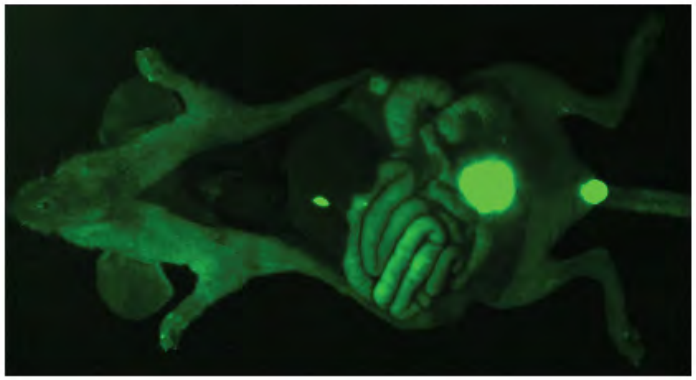
White Light



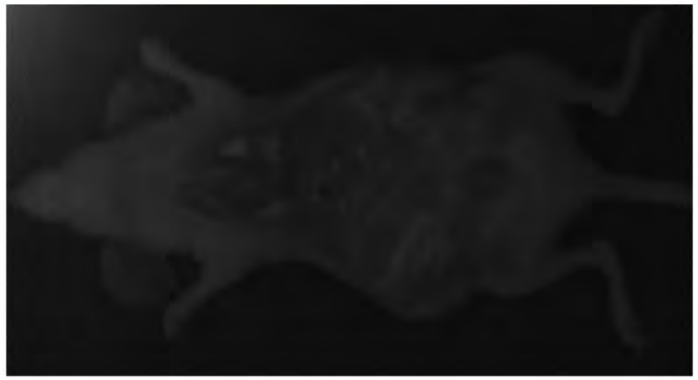
Green/ Red Filter Set



Blue/ Green Filter Set



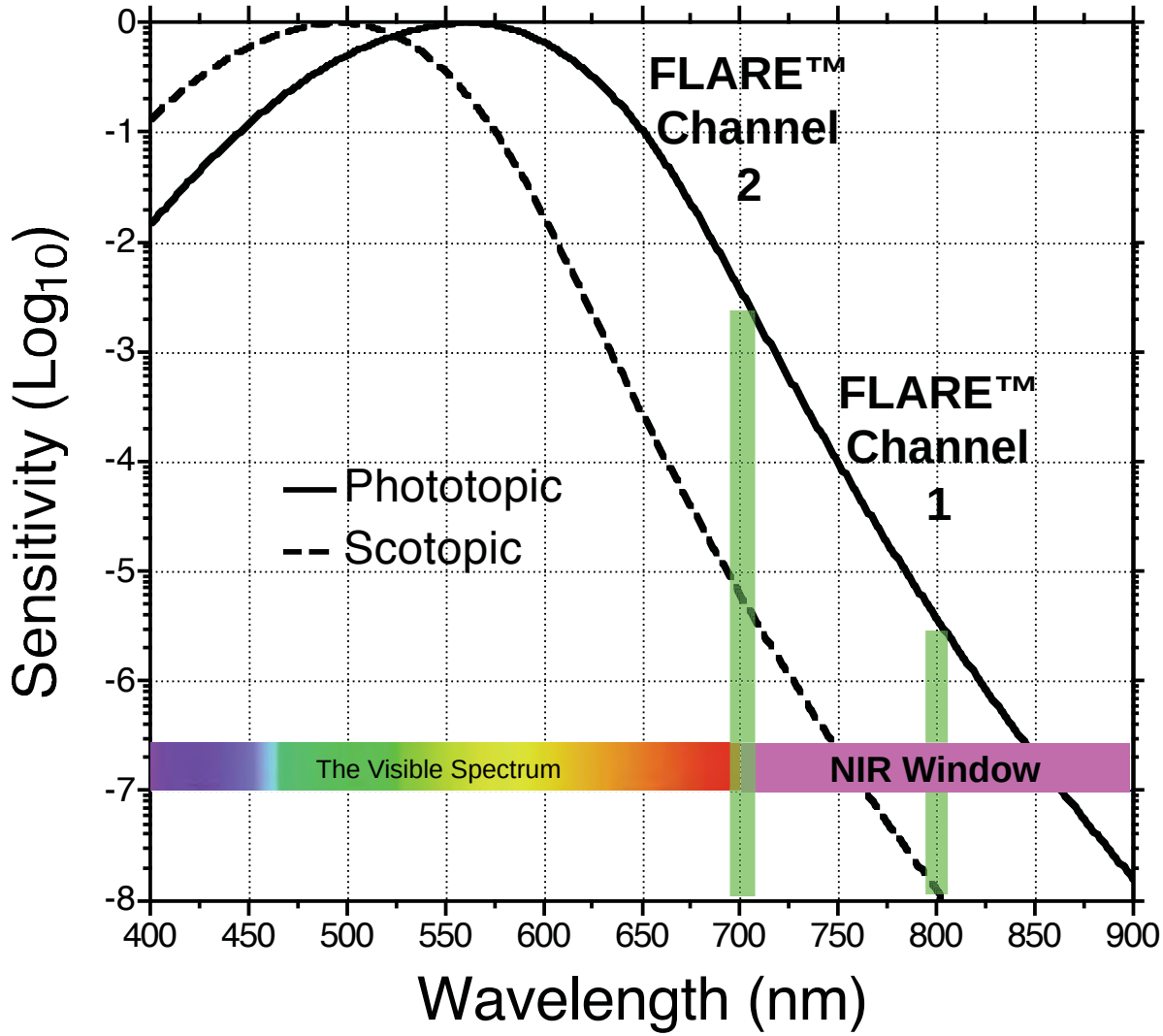
NIR Filter Set



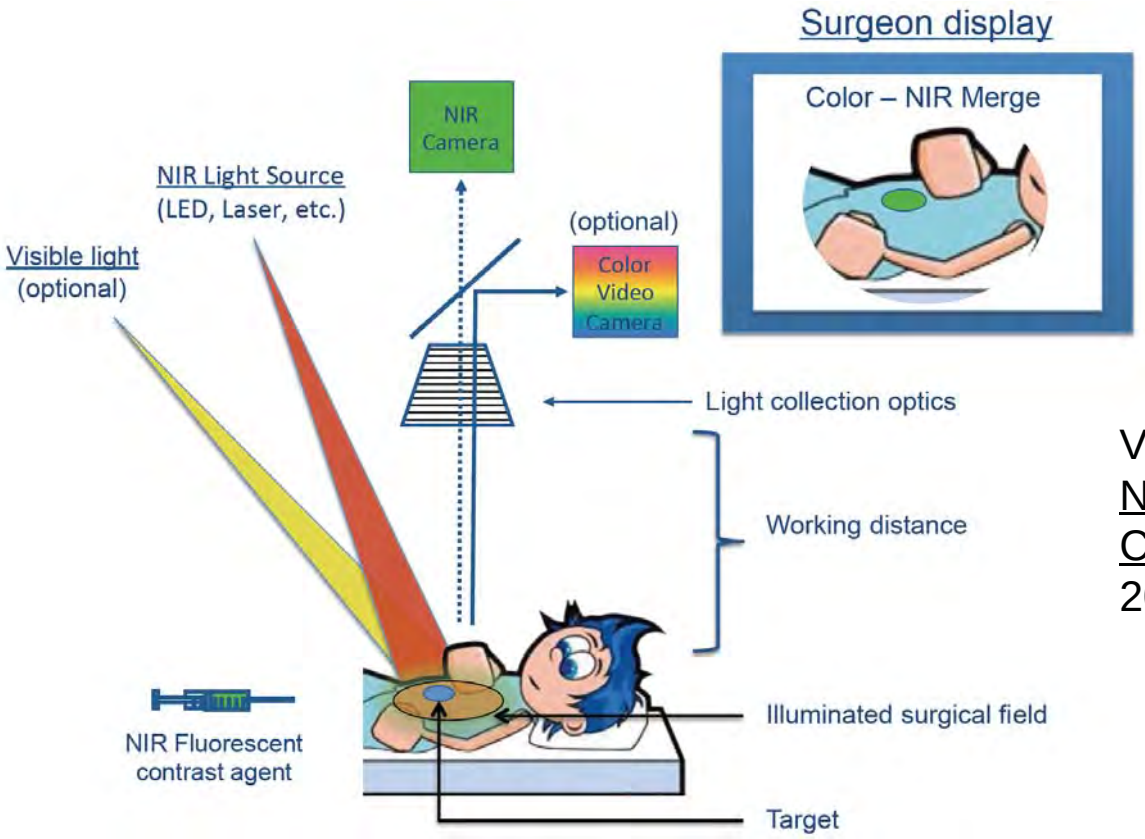
* Matched excitation fluence rates and filter bandwidths.
  Camera exposure times normalized for CCD quantum efficiency.

Frangioni Curr Opin Chem Biol. 2003; 7: 626-634.

4) NIR Light is Invisible to the Human Eye



Typical Imaging System Setup



Vahrmeijer et al., Nature Reviews Clinical Oncology, 2013; 10: 507-518.

Form Factors

Open surgery
Fiberoscopy

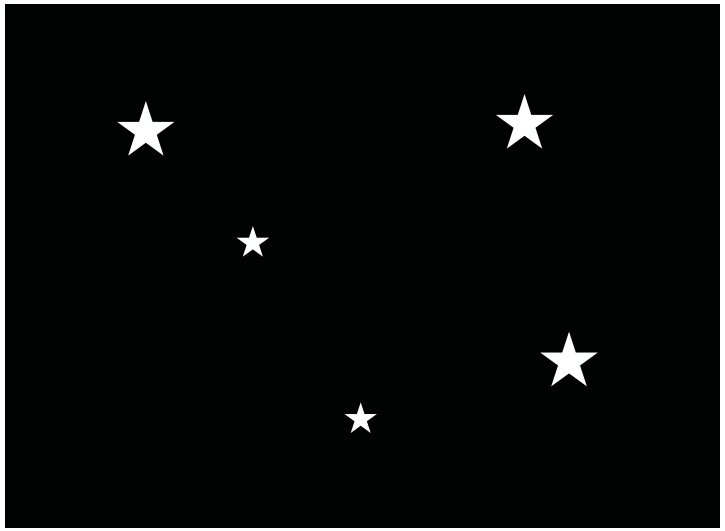
Key Parameters

Fluence rate adjusted for laser Class 3R
Fluence rate adjusted below photobleaching
NIR-compatible optics
Real-time acquisition and display

NIR Contrast: "Bright Stars on a Black Sky" **

Visible Fluorescence

NIR Fluorescence



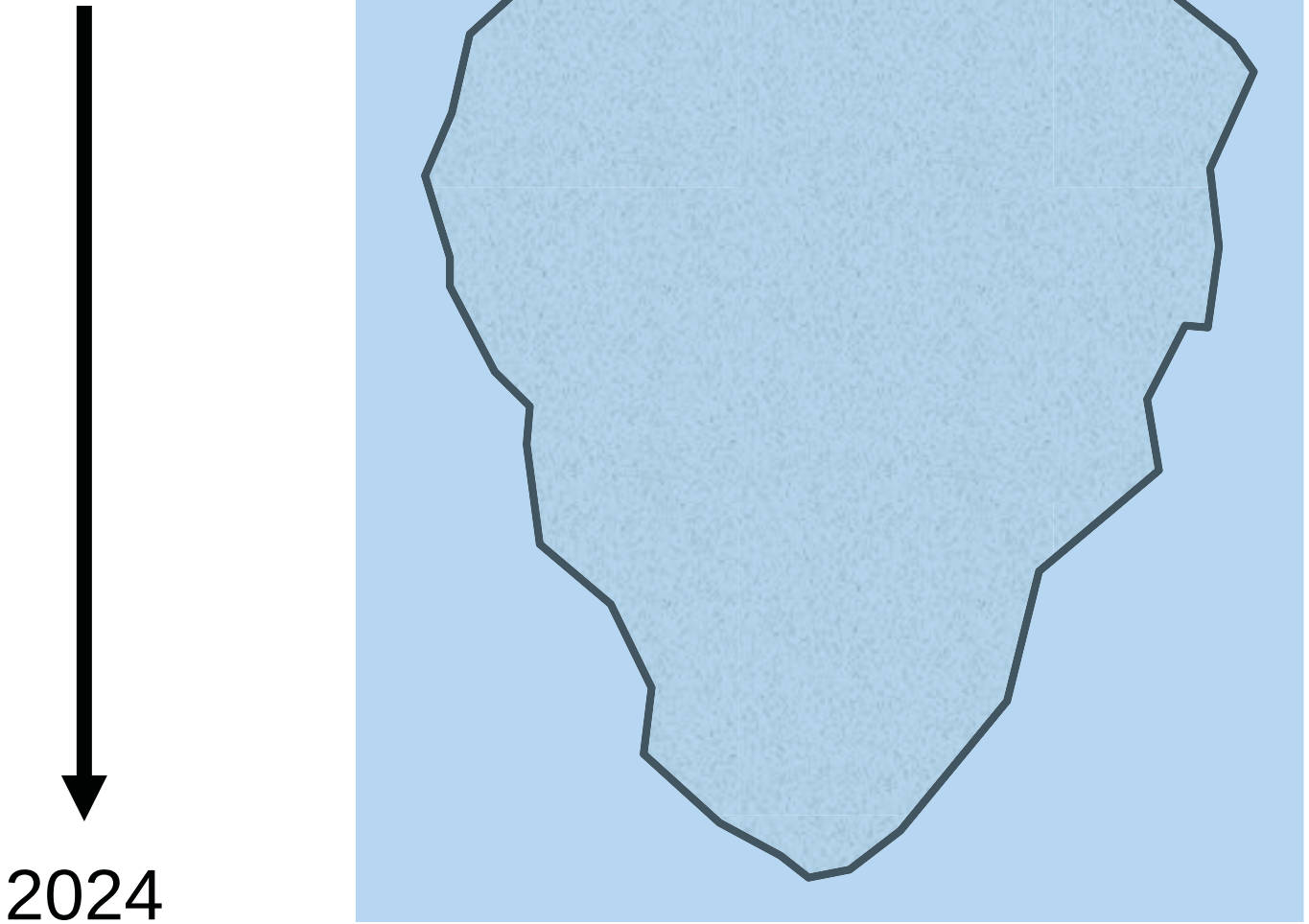
** Provided that optimal imaging systems and contrast agents are available.

So, Why all the Excitement?

- Sensitive, real-time, high-resolution tumor margin detection (deposits as small as 10 cells wide)
- Avoidance of blood vessels, nerves, ureters, bile ducts, and other vital structures during tumor resection
- Rapid identification of sentinel lymph nodes and other sub-surface structures without the need for ionizing radiation
- Reduced anesthesia time
- Lower patient morbidity from damage to vital structures
- Increase surgeon and OR throughput (raise income)
- Improved surgical outcomes lead to lower healthcare costs
- Proof of principle in over 500 patients worldwide

The Current Impact of Field is like the Tip of an Iceberg

2014



2024

Definitions

Personalized Medicine: The use of genotypic or phenotypic biomarkers to select one or more NIR fluorescent contrast agents matched to an individual patient, without regard for disease incidence (read "small market sizes").

vs.

Killer App: Either a general-purpose contrast agent that can be used for a large number of surgeries, or, a molecular-targeted agent that can be used for a single high-incidence disease (read "large market sizes").

Defining the Problem

The Key Question: Does the field of NIR fluorescence imaging want/need dozens and hundreds of targeted agents or just a few general-purpose reagents, akin to ^{18}FDG, which target major phenotypes (proliferation, metabolism, hypoxia, apoptosis, etc.)?

My Thesis: The inherent tension between personalized medicine (academic perspective) and killer apps (industry perspective) has stalled the field of NIR fluorescence-guided surgery. This tension is not unique to optical imaging, and is discussed eloquently for PET in the following review by Dr. Gary Kelloff:

"The progress and promise of molecular imaging probes in oncologic drug development" Kelloff et al. Clin Cancer Res. 2005; 11: 7967-7985.

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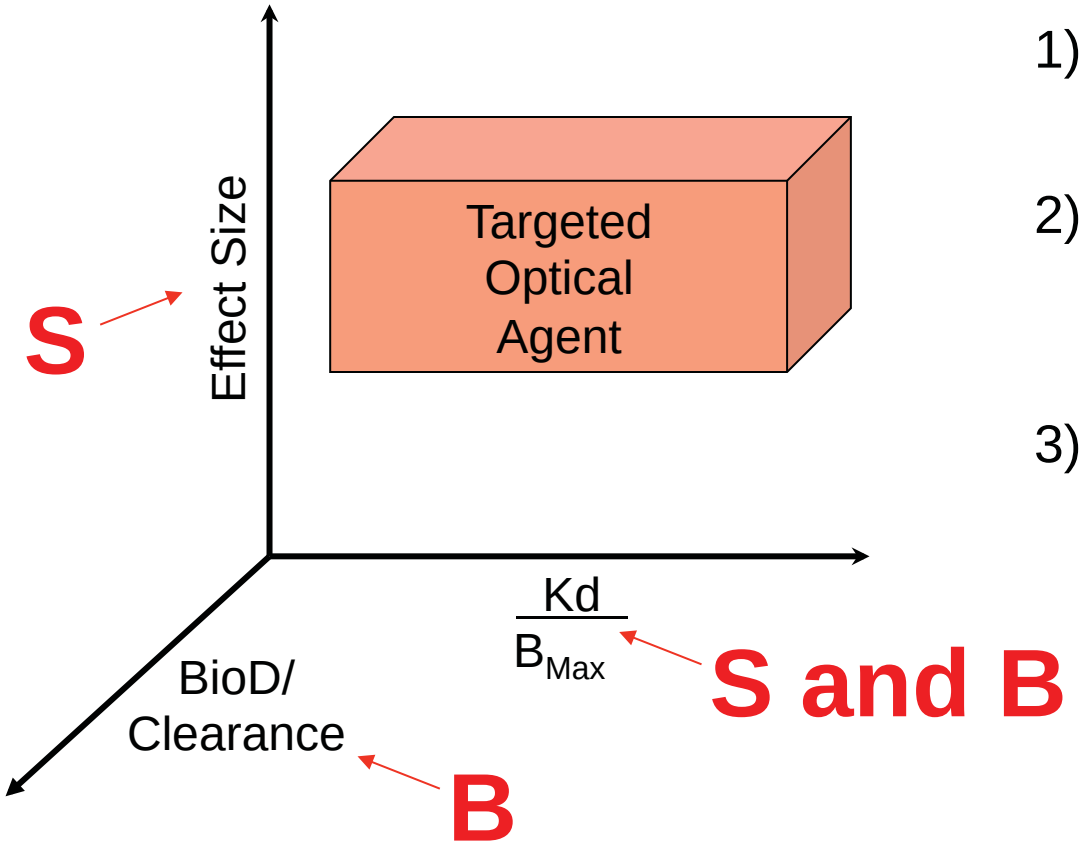
Factors Impacting the SBR of a New NIR Fluorescent Contrast Agent

A Complex, Three-Dimensional Technical Problem



1) Improved chemistry (affinity and specificity)

2) Improved chemistry (better clearance and reduced background)

3) Improved chemistry/physics (improved sensitivity)

Frangioni, J. Clin. Oncol. 2008; 26: 4012-4021.

US FDA Approvals of New Diagnostic Agents over the Last 12 Years (and Still Marketed)

Year	Generic Name	Targeted	Indication
2002	None		
2003	None		
2004	^{18}Fluorodeoxyglucose (FDG)	No	Cancer imaging (Weill Med Coll)
	Gadobenate dimeglumine	No	I.V. MRI contrast (Blood Pool)
2005	None		
2006	None		
2007	^{13}N-ammonia	No	PET imaging of perfusion
2008	Gadoxetate disodium	No	I.V. MRI contrast (liver/kidneys)
	Gadofosveset trisodium	No	I.V. MRI contrast (Blood Pool)
2009	None		
2010	Hexvix	Yes	Bladder cancer visualization
2011	^{123}I-Ioflupane	Yes	Parkinson's disease
	Gadobutrol	No	I.V. MRI contrast (BBB disruption)
2012	^{18}F-Florbetapir	Yes	Alzheimer's plaques
	^{11}Choline	No	Prostate cancer
2013	^{99m}Tc-Tilanocept	Yes	Sentinel lymph node mapping
	Gadoterate	No	I.V. MRI contrast (BBB disruption)
	^{18}F-Flutemetamol	Yes	Alzheimer's plaques
	Total:	**13**	**(≈ 1 new agent per year; 5/13 GBCA; only 5/13 targeted)**

Patient Access to New Diagnostic Agents

From MICAD Database (compiled by Dan Sullivan, Duke; 10/13)

"The 0.2% Rule"

≈5,361 Number of molecular imaging agents in the peer-reviewed literature

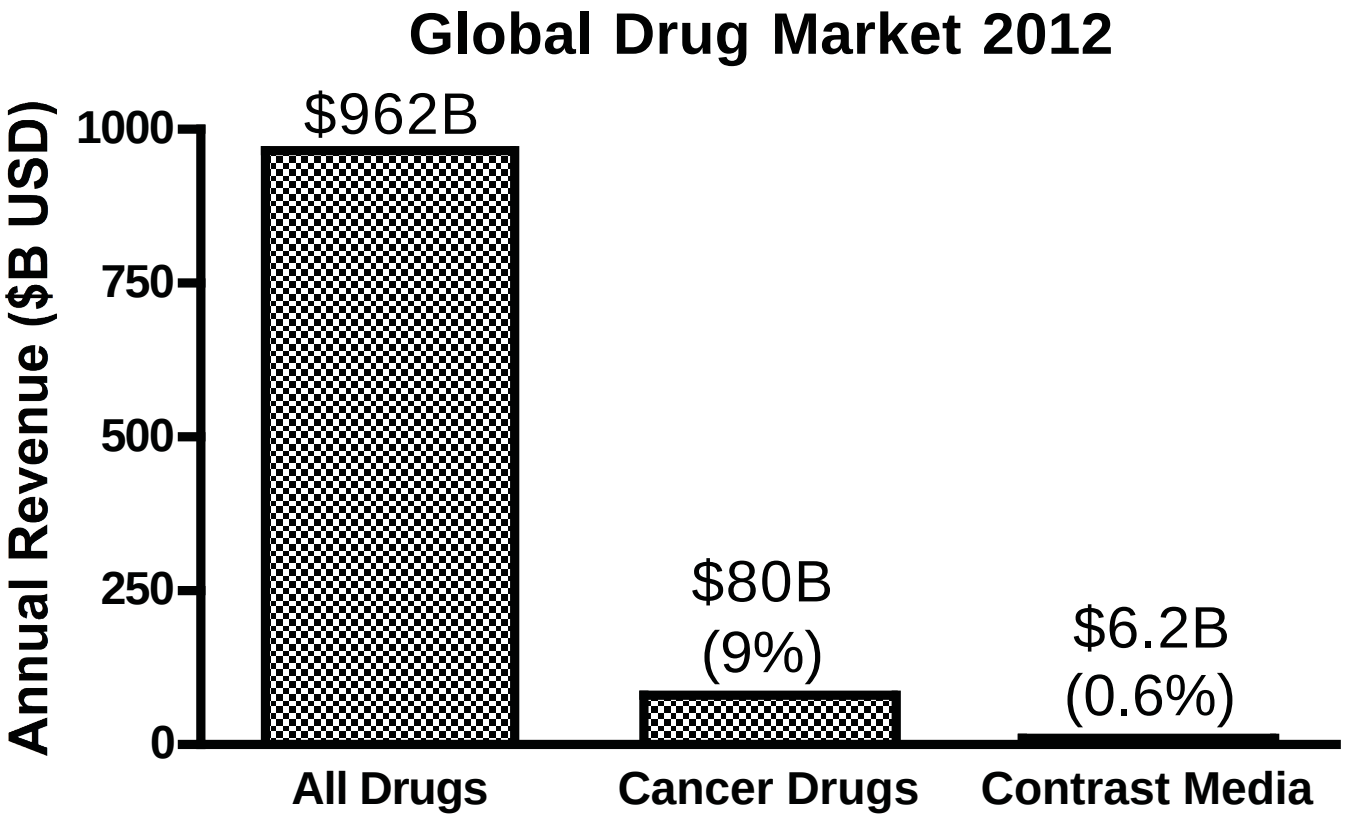
≈464 Number of agents actually tested in humans

≈ 13 Number of new FDA-approved diagnostic agents in the last 12 years

State-of-the-Art in 2014

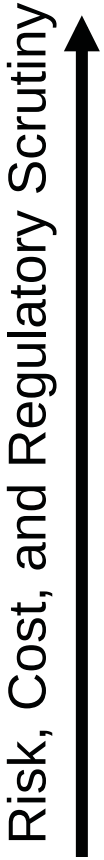
Of the 123 FDA-approved *in vivo* diagnostic agents on the market today, there are only **≈ 20** different classes (virtually all non-disease-specific) available for routine clinical care in children and adults to diagnose all known human diseases. And, these agents are spread among CT, MRI, SPECT, PET, and US.

Molecular Imaging A Speck of a Market



Average annual revenue of the 123 approved agents is only $50M!

Typical Doses of Intravenously Administered Diagnostic Agents and Radiotracers from High (CT) to Low (PET)



Imaging Modality	Human dose (g)
CT	75 cc of 930 mM solution (≈ 800 Da) = **56 g**
MRI	15 cc of 500 mM solution (≈ 940 Da) = **7 g**

2 regular-strength acetaminophen (bioavailable dose) = 600 mg

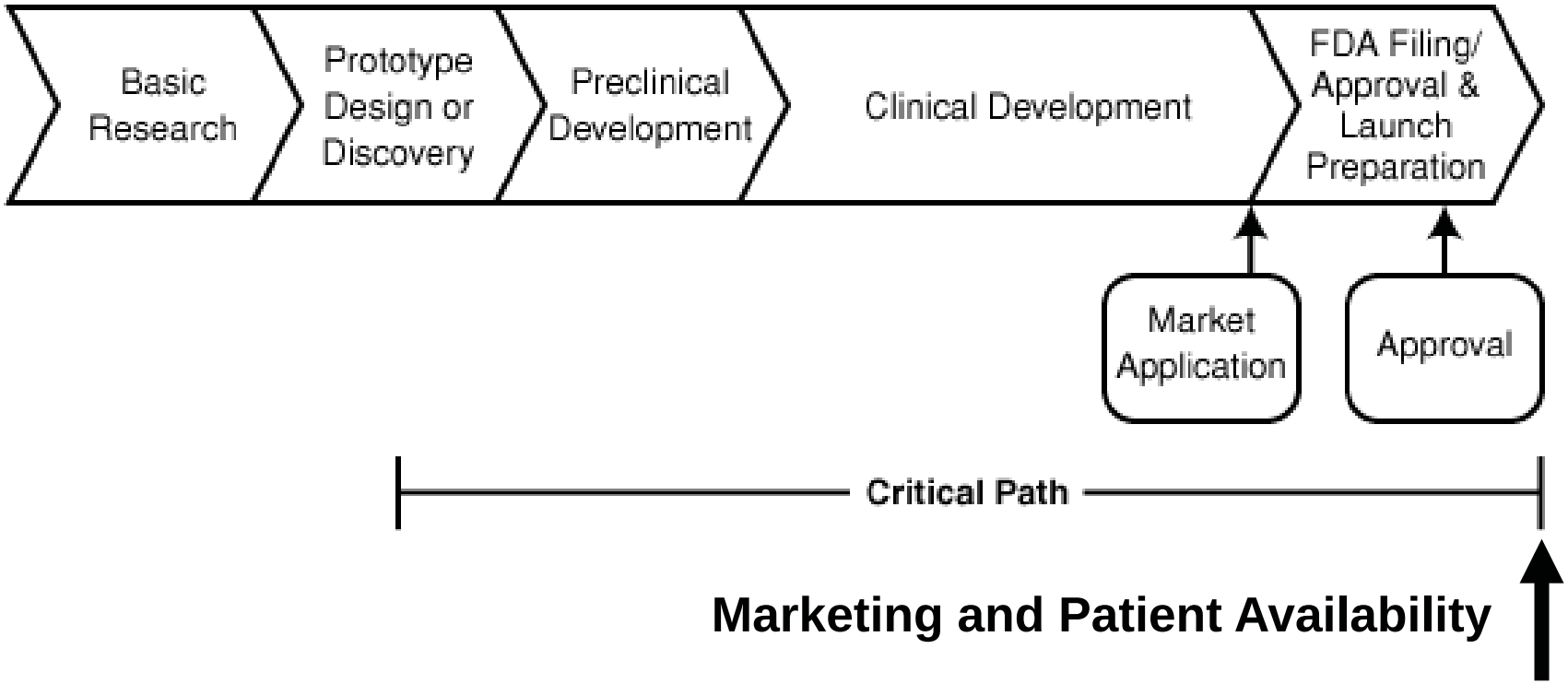
Optical	≈ 10 cc of 1 mM solution (≈1,000 Da) = **10 mg**

FDA definition of “micro-dosing” = 100 µg

SPECT	20 mCi (10,000 Ci/mmol; ≈500 Da) = **1 µg**
PET	20 mCi (10,000 Ci/mmol; ≈500 Da) = **1 µg**

Gioux et al., Mol Imaging. 2010; 9: 237-255.

The Critical Path Initiative



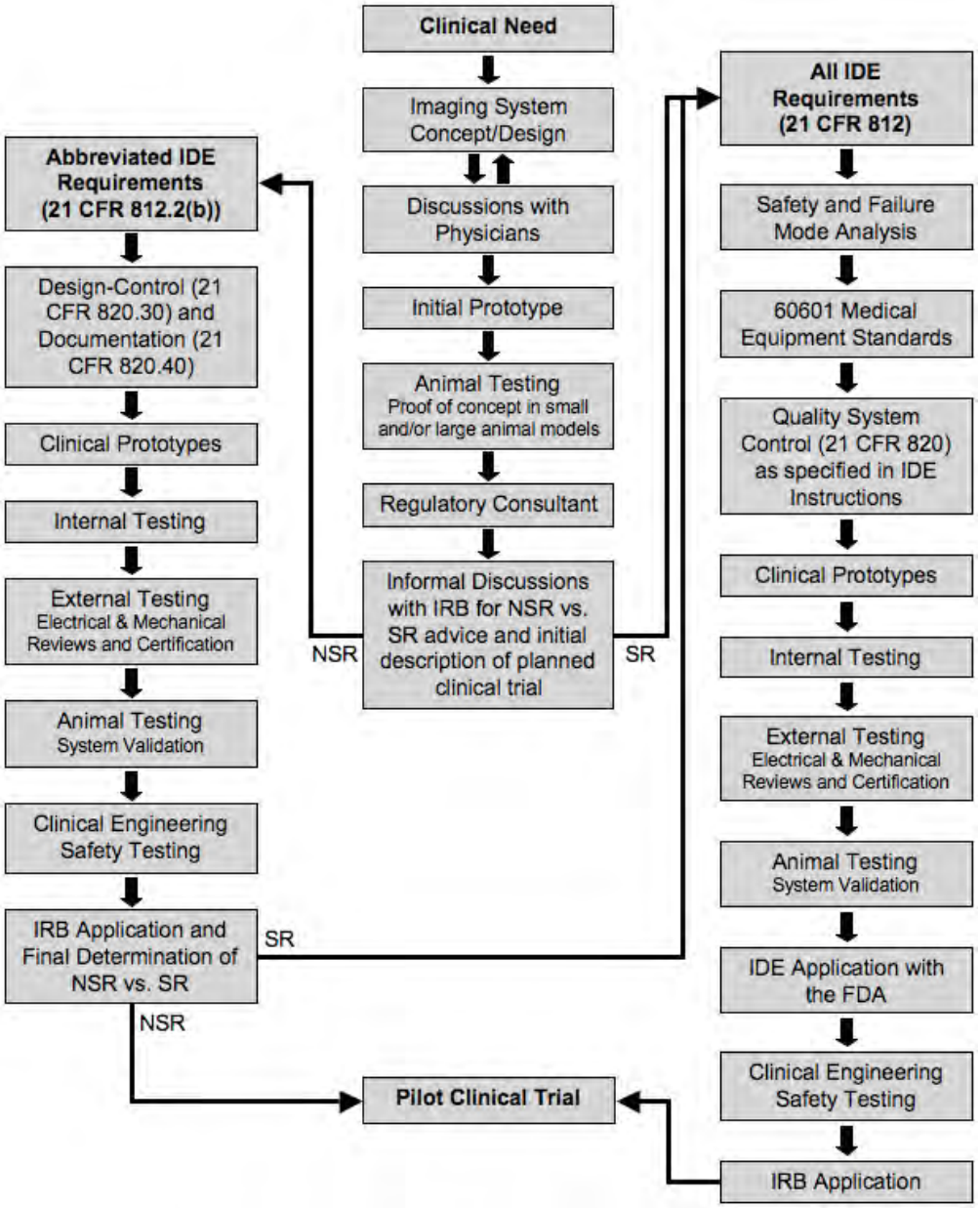
Logarithmic Scale in Terms of Time, Money, and Effort

Basic Research through First-in-Human Trial (Translation)

Everything Else (Commercialization)

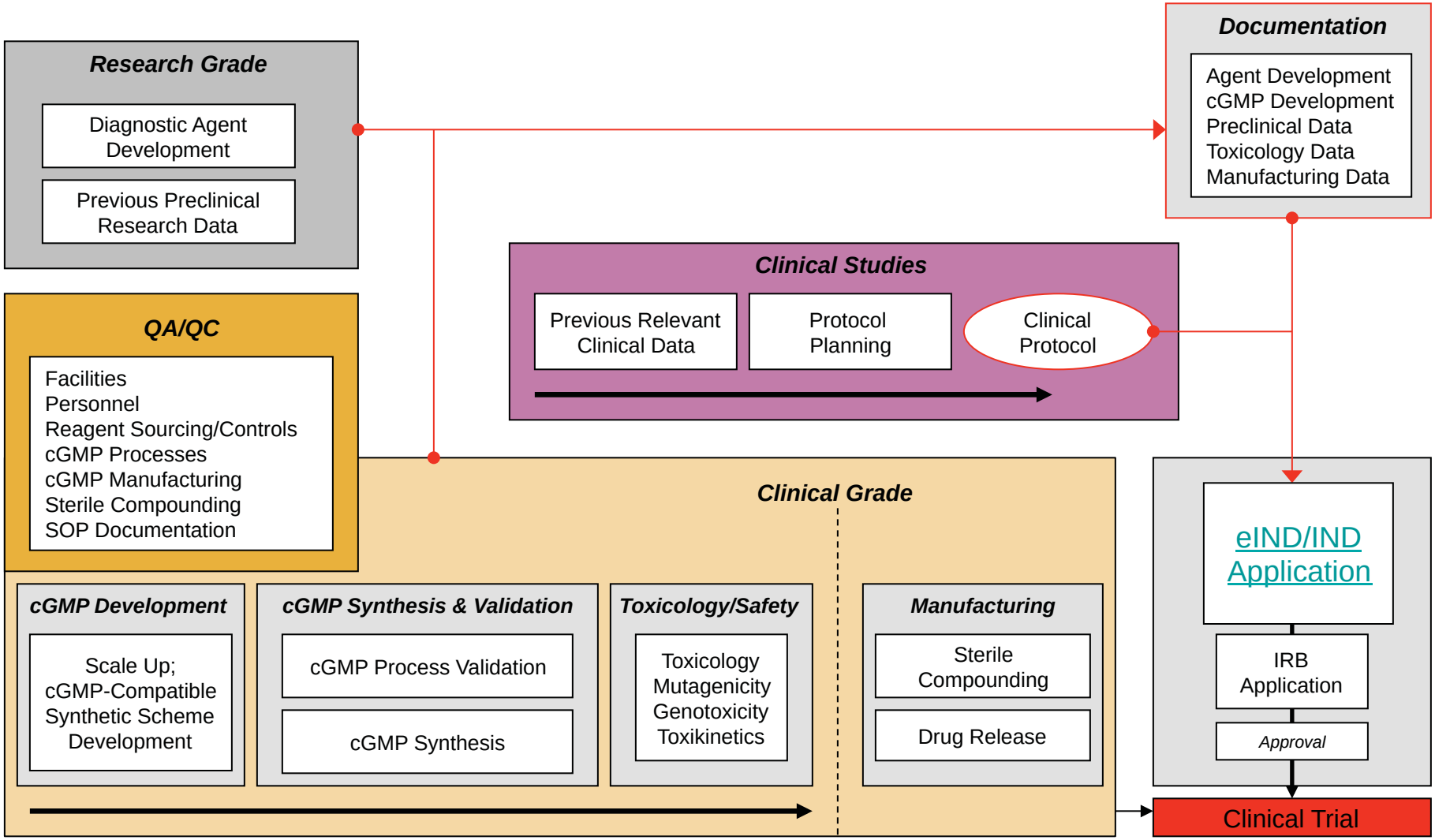
Linear Scale in Terms of Time, Money, and Effort

The "Risk Conundrum" for First-in-Human Device Trials



Gibbs-Strauss et al.,
IEEE Eng Med Biol, 2009.

The FDA IND Process for First-in-Human Drug Trials



Why are Diagnostic Agent Approvals so Rare?

Contribution	Barrier
5%	Science and engineering
5%	Pre-clinical and first-in-human studies
35%	Economic:
	Market size
	Cost of approval process
	Cost of “time”
35%	Regulatory:
	ISO 13485 (Devices)
	ICH Q10 (Contrast Agents)
	Institutional Review Board (IRB)
	Food & Drug Administration (FDA)
	European Medicines Agency (EMEA)
20%	Integration into clinical workflow:
	Physicians and Surgeons
	Nursing and Allied Health Professionals

Why are Diagnostic Agent Approvals so Rare?

Time and Money (Per Agent)

Milestone	Approx. Cost	Approx. Time
Phase I	$0.3-1M	6-12 months
Phase II	$5-10M	1-2 years
Phase III	$30-50M	2-3 years
Total:	**$35-61M ****	**3.5-6 years**

** As high as $200M for high-dose MRI/CT agents

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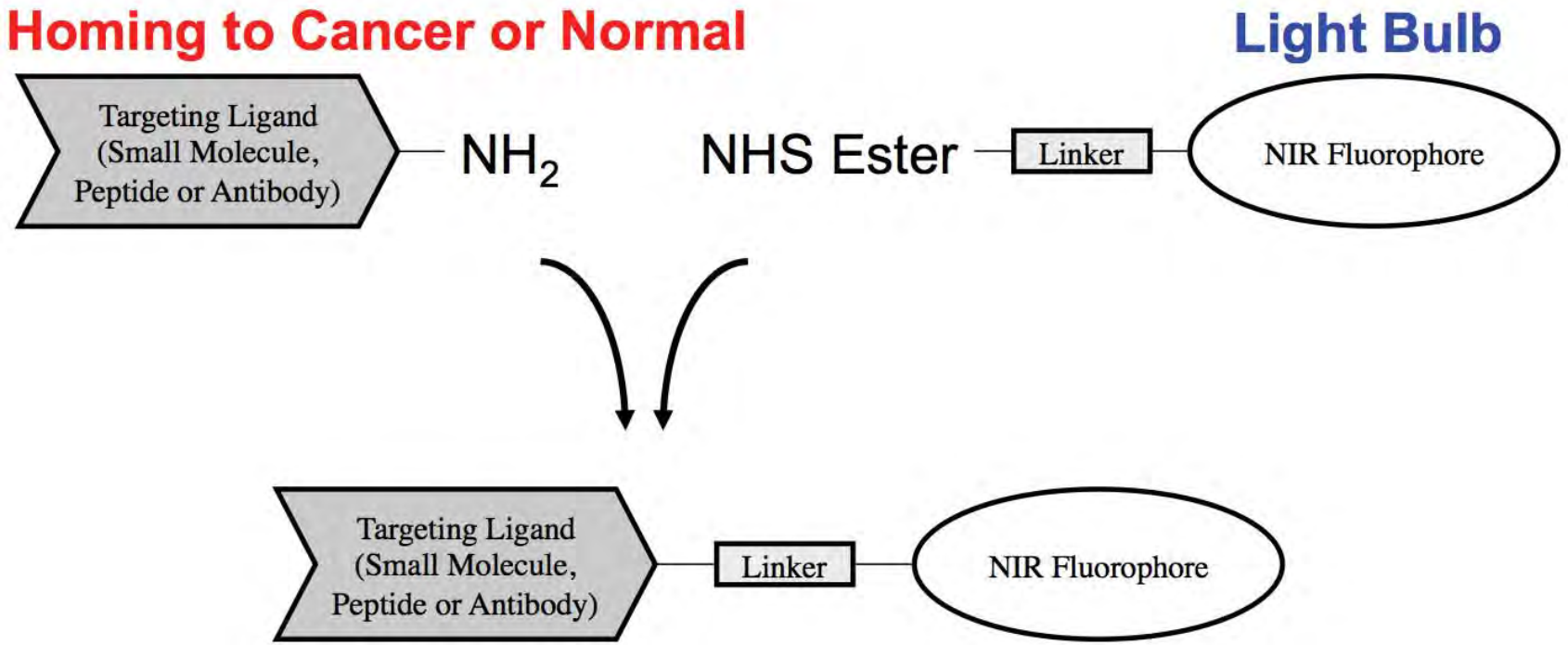
The Personalized Medicine (Academic) Perspective

- Enabled by innovations in genomics and proteomics
- Optical imaging is one of the few cases where a single NIR fluorophore can be used to create dozens and hundreds of patient-/tumor-specific targeted contrast agents.



But Here are the Problems

- Personalized medicine fragments market share
- $30-60M upfront investment per agent

Number of Surgical Cases per Year	Price per Dose	Annual Gross*
10,000	$250 / $500	$2.5M / $5M
25,000	$250 / $500	$6.3M / $12.5M
50,000	$250 / $500	$12.5M / $25M
100,000	$250 / $500	$25M / $50M

* Annual Net is only 25-75% of Annual Gross

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Industry Says: General-Purpose Reagents or High-Incidence Diseases

- Sentinel lymph node mapping: potentially 1M cases/year (but, can be done reasonably well for ≈ $75 per case)
- Nerve imaging: potentially 1M cases/year
- Angiography: potentially 50,000-100,000 cases/year (but, can be done now for ≈ $75 per case)
- Breast cancer: potentially 100,000 cases/year
- Prostate cancer: potentially 100,000 cases/year

Number of Surgical Cases per Year	Price per Dose	Annual Gross*
100,000	$250 / $500	$25M / $50M
1,000,000	$250 / $500	$250M / $500M

* Annual Net is only 25-75% of Annual Gross

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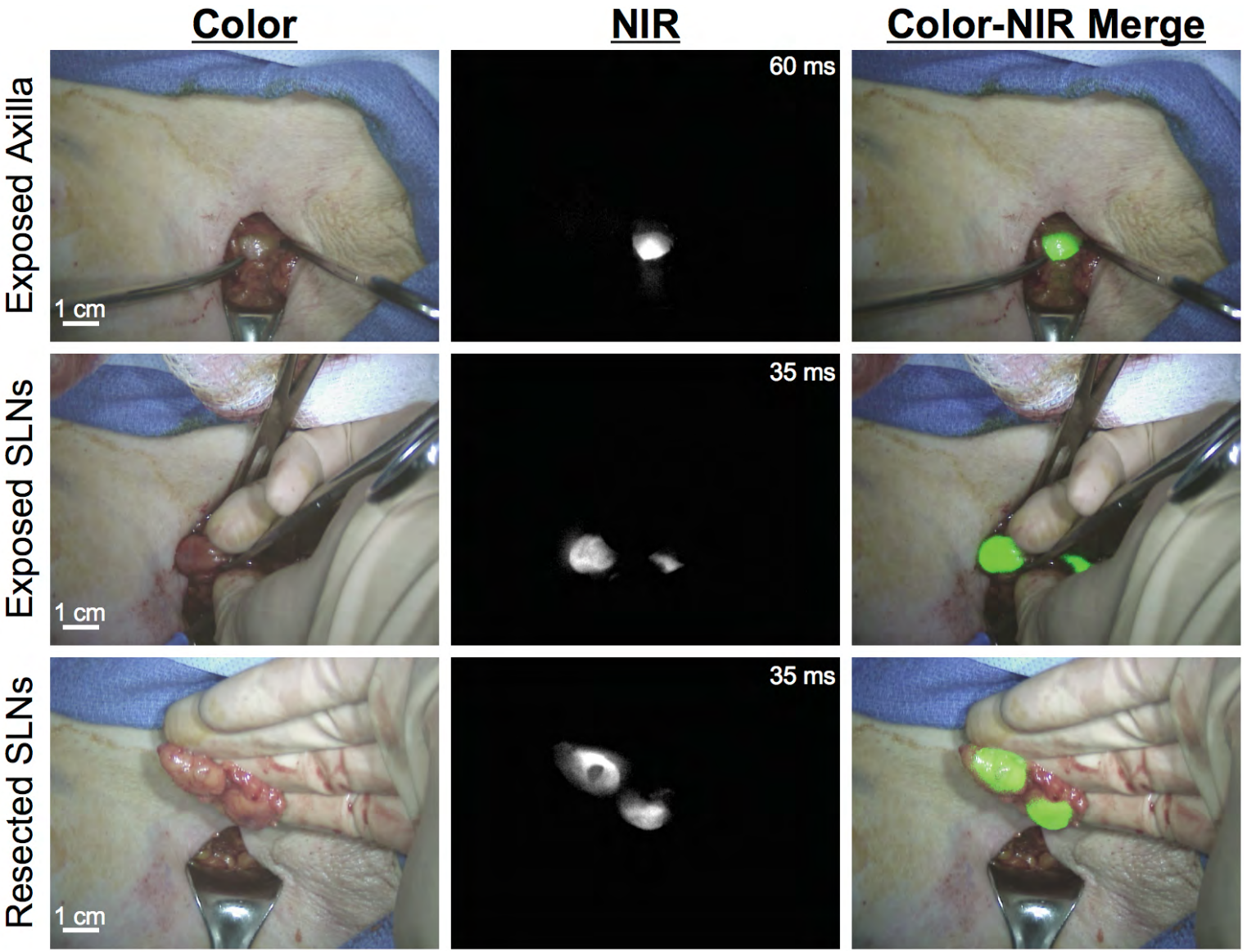
The Critical Objective Test for New Medical Technology

Will it improve patient management?

And Not… Is there a clinical need?
…necessary but not sufficient
Is it possible to do?
Is it exciting to do?
Is it state-of-the-art engineering, chemistry, and/or surgery?

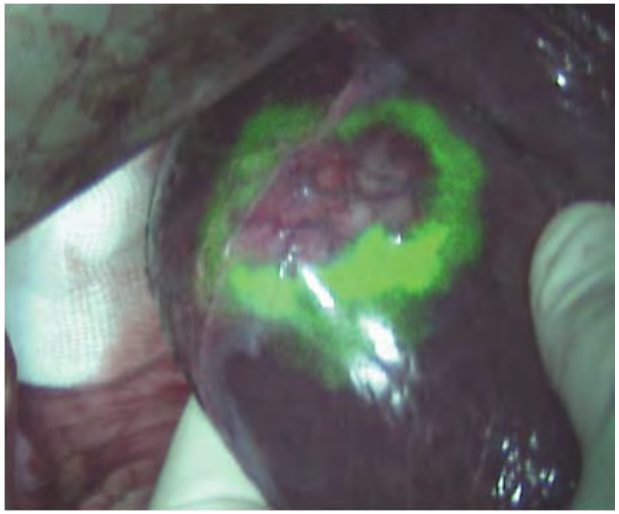
NIR Fluorescence appears to satisfy this criterion.

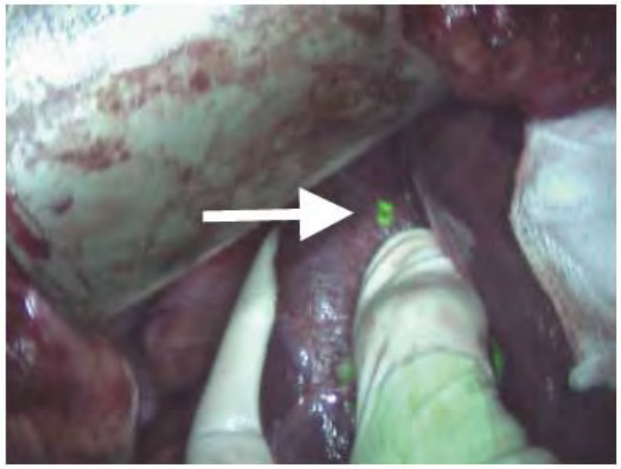
ICG: Breast Cancer



Mieog et al., Ann Surg Onc. 2011; 18: 2483-2491.

ICG: Colon Cancer Hepatic Metastases





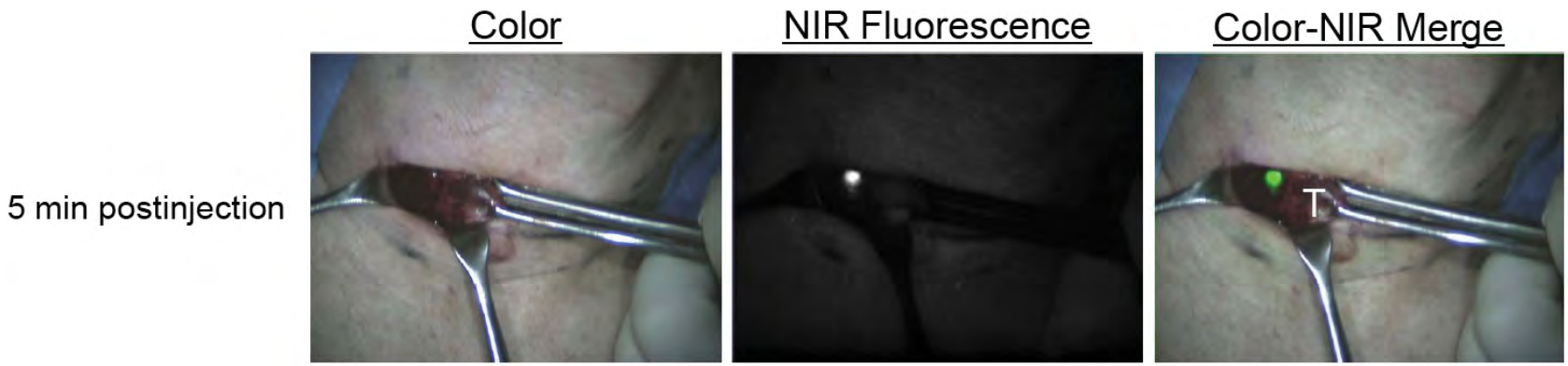
van der Vorst et al., Cancer. 2013; 119: 3411-3418.

Real-time identification of colorectal liver metastases in 22 patients undergoing liver resection.

NIR fluorescence imaging was performed 24 or 48 h after administration of 10 or 20 mg ICG.

5 of 40 small, superficial metastases not detectable by ultrasound or palpation

Methylene Blue: Parathyroid Tumor Imaging



van der Vorst et al., Head and Neck. 2013; *In Press*

The Answer to the Initial Question

The Key Question: Does the field want/need dozens & hundreds of targeted agents or just a few general-purpose reagents akin to ^{18}FDG that target major phenotypes (proliferation, metabolism, hypoxia, apoptosis, etc.)?

My Answer: "It depends"

Think of it like enzyme kinetics.

Early in the evolution of an imaging field, where we are now for NIR-guided surgery, we need Killer Apps to entice investment, prove that commercialization can be profitable, and create a worldwide market. Killer apps are the ***catalyst*** and open up the capital markets for a new technology.

Experience with killer apps will then create efficiencies in the device and drug development process, and mitigate risk, such that cost-to-market can be greatly reduced. At some as yet undefined per-agent cost, virtually any personalized contrast agent becomes profitable and thus viable. Personalized agents are the ***substrate*** for sustaining a technology.

The Field of NIR Fluorescence-Guided Surgery

→ Full Throttle (Academia)

\+

← Full Brake (Industry)

The History of Clinical Translation in Diagnostics

"What we learn from history is that people don't learn from history." Warren Buffett

Modality	First Patient	Clinical Acceptance	Lag
PET	1953	≈ 2003	≈50 years
Plain Films (X-rays)	1895	≈ 1920s	≈ 25 years
SPECT	≈1963	≈ 1985	≈23 years
US	≈1940s	≈ 1960s	≈ 20 years
MRI	1970	≈ 1985	≈15 years
CT	1967	≈ 1975	≈7 years
NIR Fluorescence	1999	? ?	15+ years

mean = 23; median = 22 yrs

FLARE™ Imaging Network

Beth Israel Deaconess Medical Center, Boston
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R21/R33-CA-88245

R21-CA-110185

DOE DE-FG02-01ER63188

CIMIT Awards (4)

Doris Duke Charitable Foundation

CaPCURE

Relevant Reviews

Vahrmeijer et al. **Image-guided cancer surgery using near-infrared fluorescence.** Nature Reviews Clinical Oncology. 2013; 10: 507-518.

Gioux, Choi, & Frangioni. **Image-Guided Surgery with NIR Light: Fundamentals of Clinical Translation.** Mol Imaging., 2010; 9: 237-255.

Frangioni JV. **New technologies for human cancer imaging**. J. Clin. Oncol. 2008; 26: 4012-21.

Gibbs et al. **First-in-human clinical trials of imaging devices: An example from optical imaging.** Proc IEEE Eng Med Biol Soc. 2009; 1: 2001-4.

Frangioni JV. **Translating *In Vivo* Diagnostics into Clinical Reality**. Nature Biotechnol. 2006; 24: 909-13.