In Vivo Applications of Near-Infrared Quantum Dots

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Outline

I. The Clinical Problem

II. The Nanotechnology Solution

III. The Regulatory Conundrum

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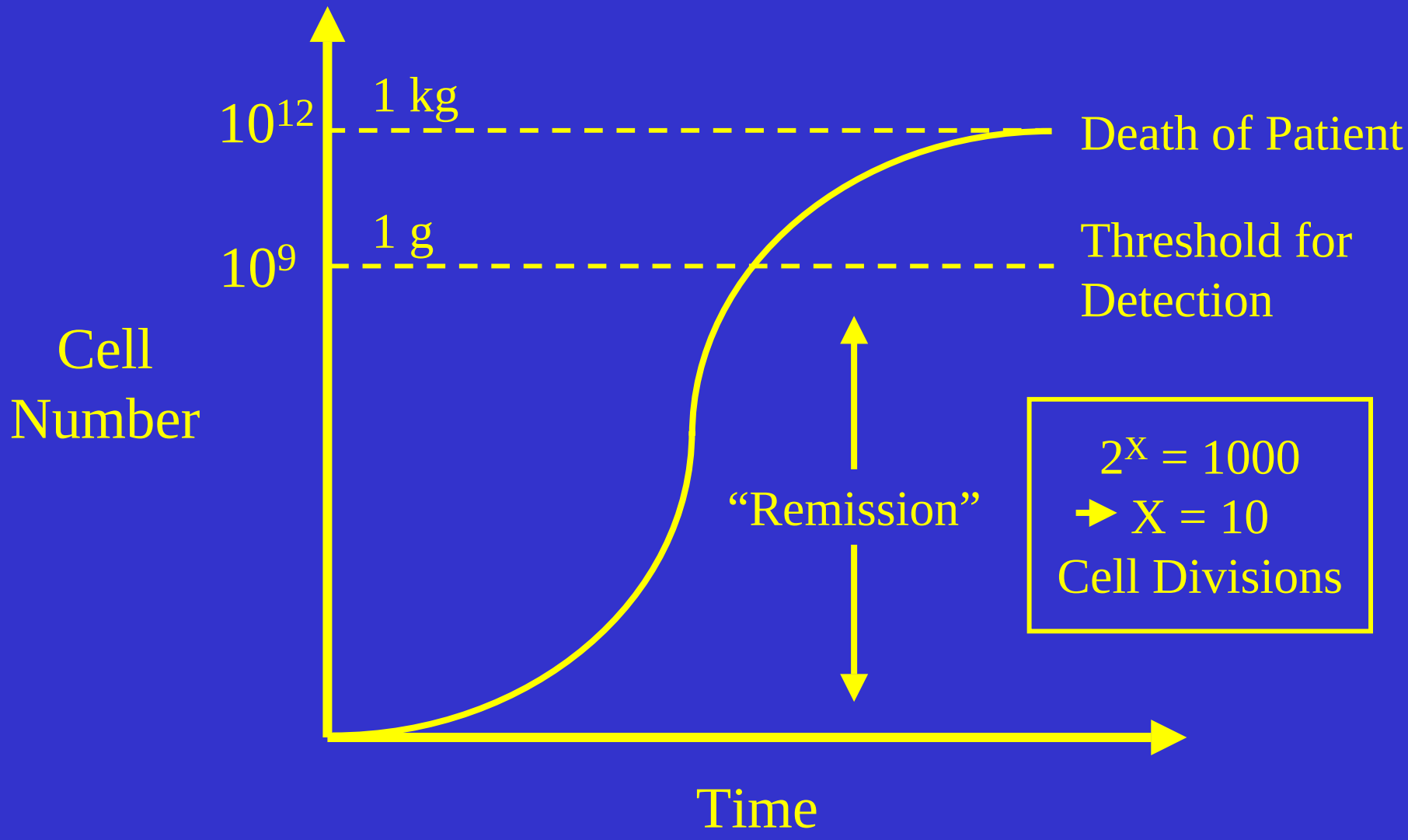
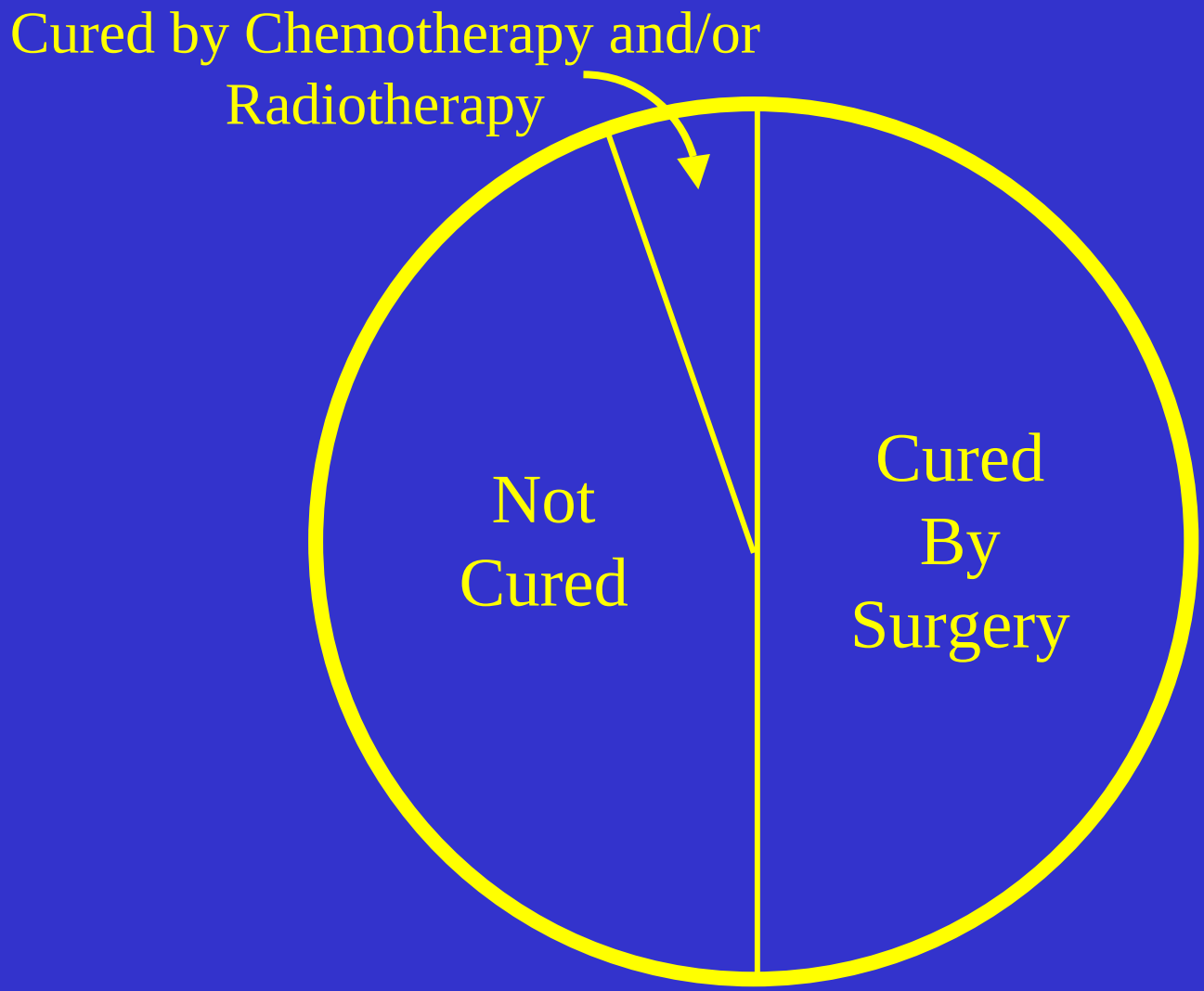
The Cancer Detection Problem

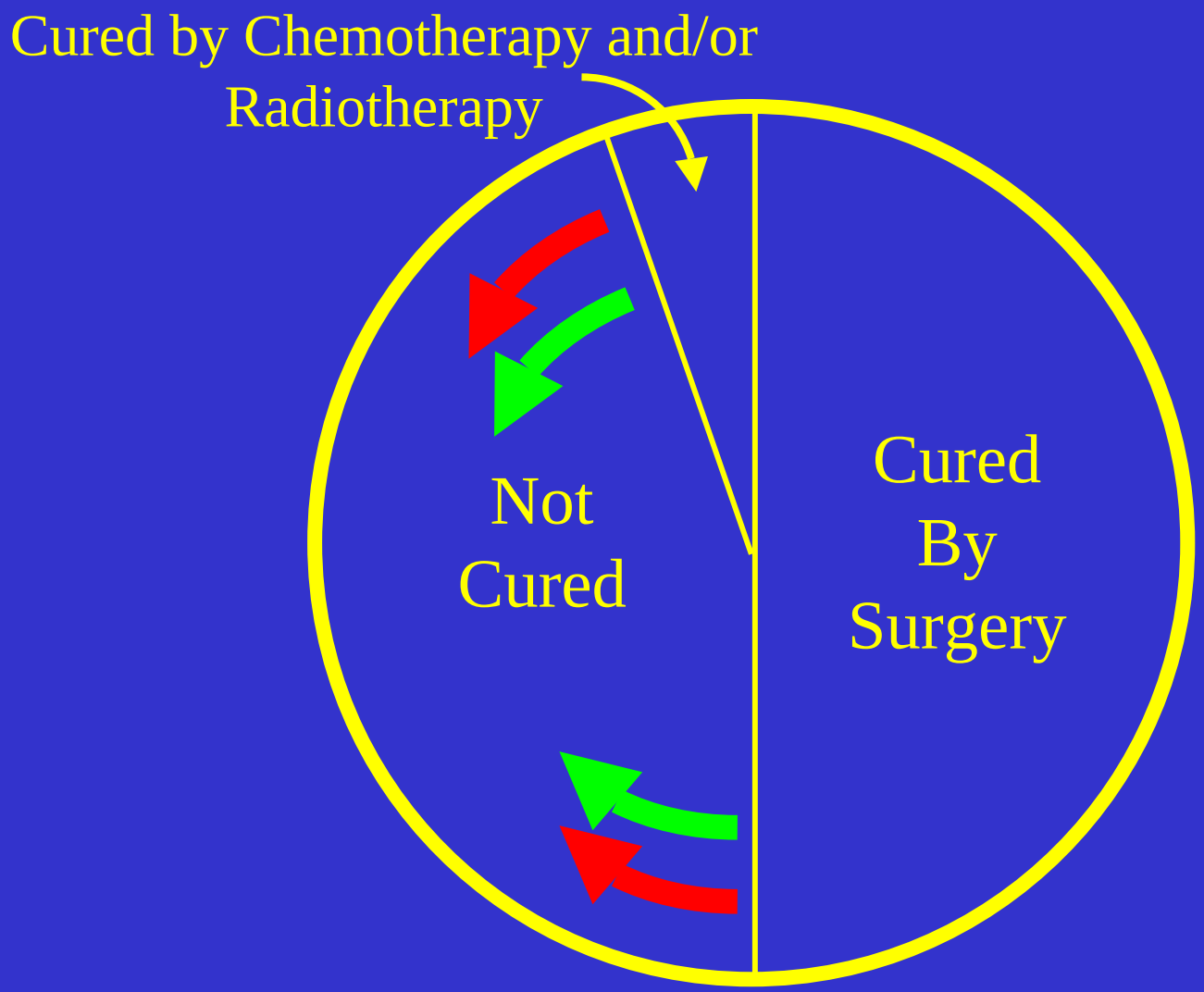


Cancer Fates in the United States



Approximately 1.3 x 10^6 Non-Skin Cancers Diagnosed
Each Year in the U.S.

Cancer Fates in the United States



Chemistry (Molecular Targeting)

Engineering (Instrumentation)

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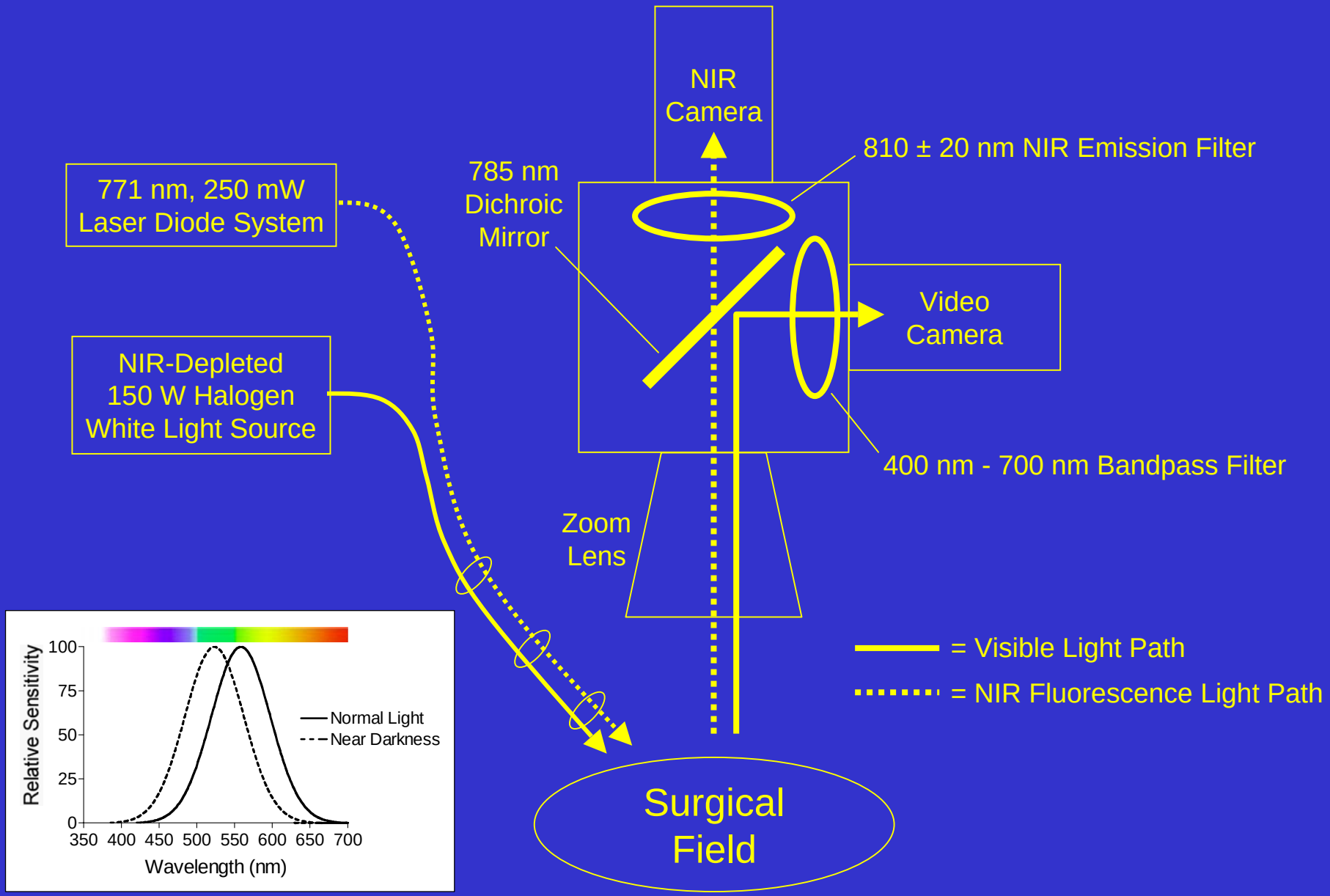
The Nanotechnology Solution Requires the Synergy of:

Engineering: Intraoperative Near-Infrared Fluorescence Imaging System

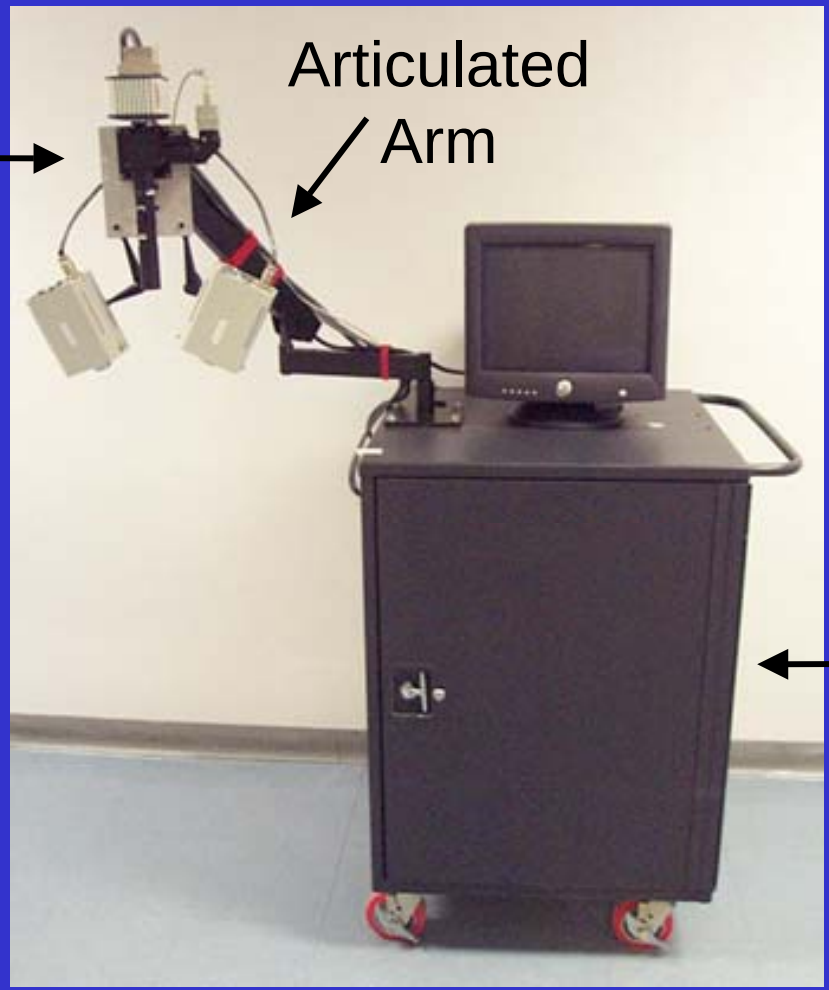
Chemistry: Highly Sensitive, Properly-Sized, and Stable Near-Infrared Fluorescent Contrast Agents (Quantum Dots)

Near-Infrared Fluorescent Surgical Imaging System



† Nakayama et al., Mol. Imaging, 2002; 1(4): 365-377

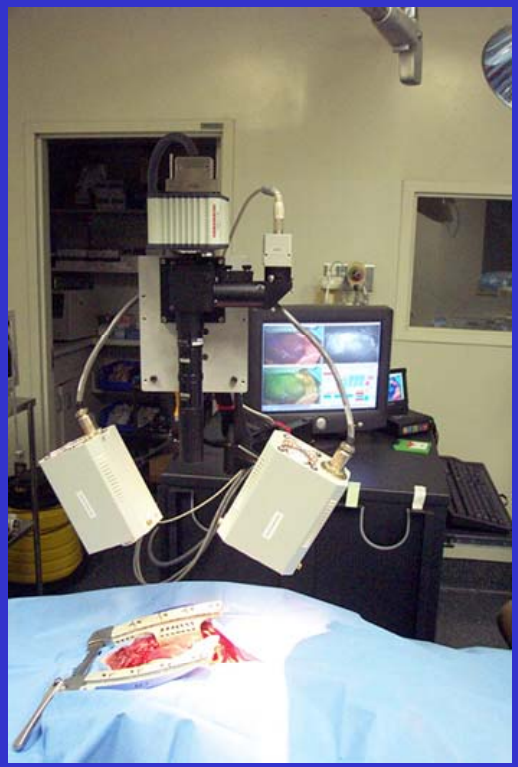
Mobile Large Animal Intraoperative Imaging System



† DeGrand & Frangioni, Submitted

Deployment in the Surgical Suite

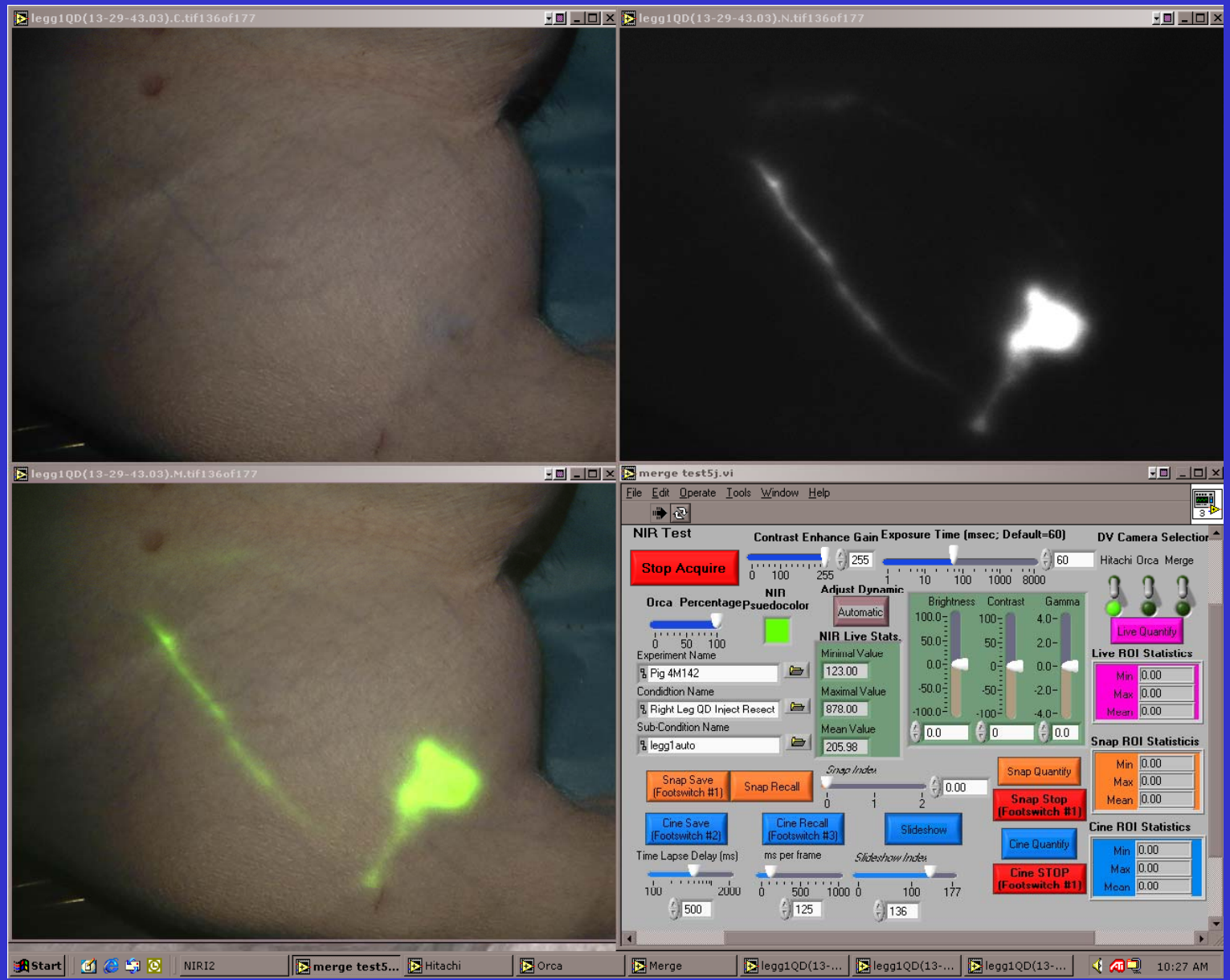
A.



B.

† DeGrand & Frangioni, Submitted

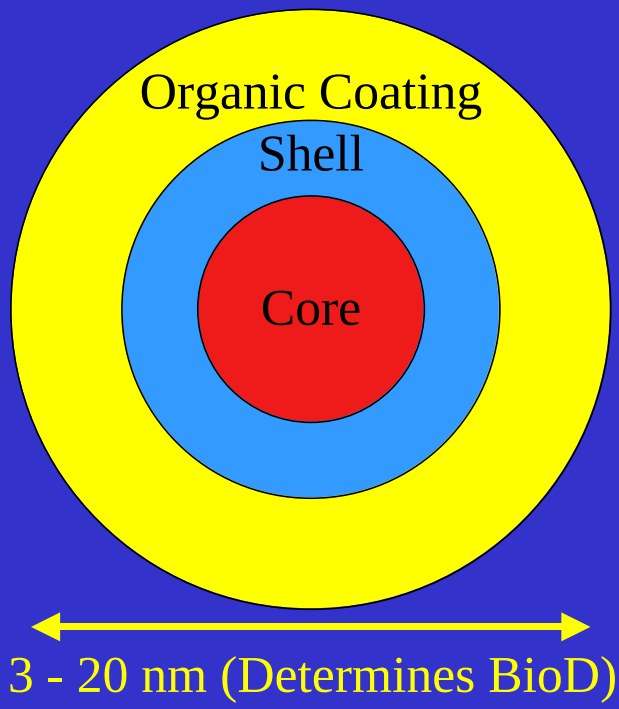
The Surgeon's View



† DeGrand & Frangioni, Submitted

Fluorescent Semiconductor Nanocrystals (Quantum Dots)

M.G. Bawendi and S.J. Kim (MIT)



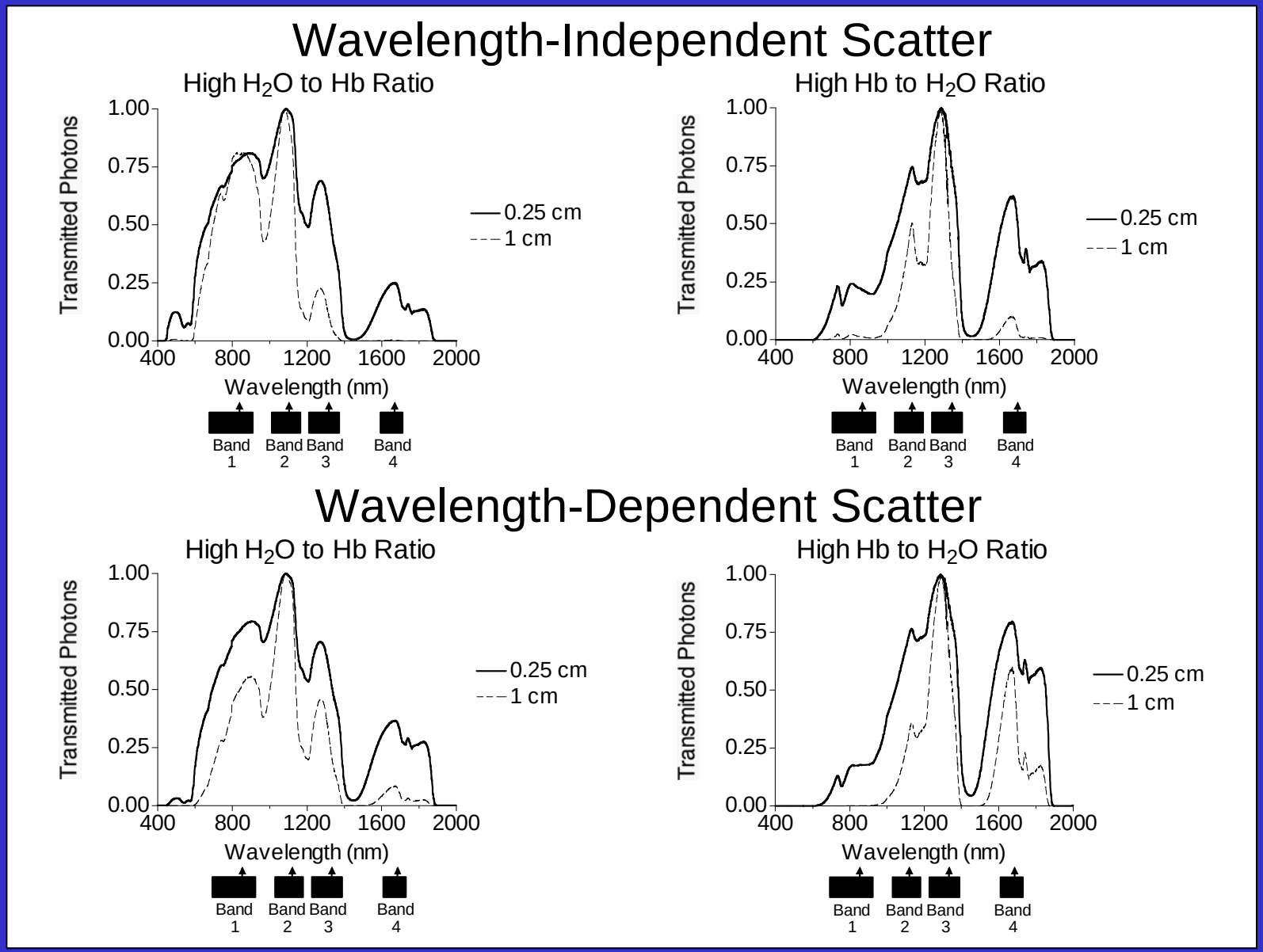
Potential Advantages

Peak emission tunable anywhere from UV to IR
High non-aqueous QYs
Broadband absorption increasing to the blue
High photostability
Conjugatable to tumor targeting ligands

Potential Disadvantages

Potential toxicity of materials
Difficult to synthesize
Size/material limitations (?solved)

Modeling of Near-Infrared and Infrared Photon Transmission

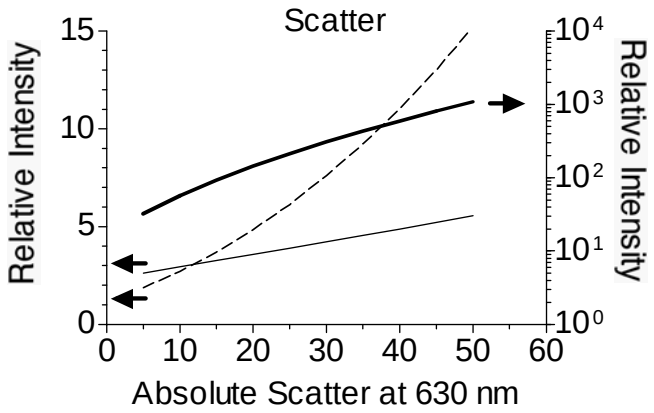


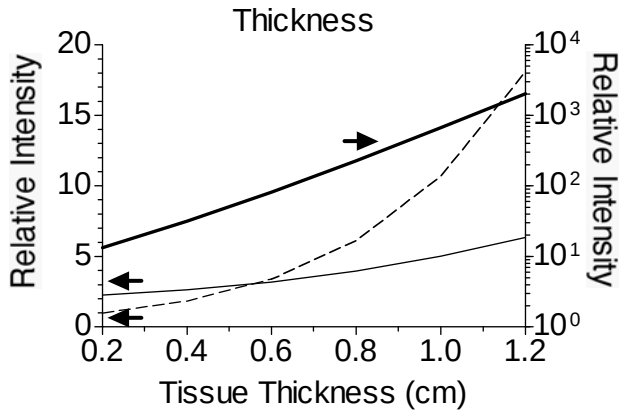
† Lim et al., Mol. Imaging, 2003; 2(1): 50-64

Infrared (1320 nm) QDs vs. NIR (840 nm) QDs

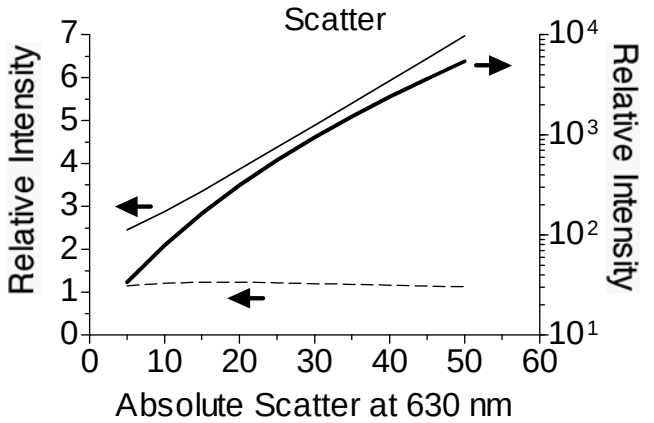
High Hb to H_2O Ratio

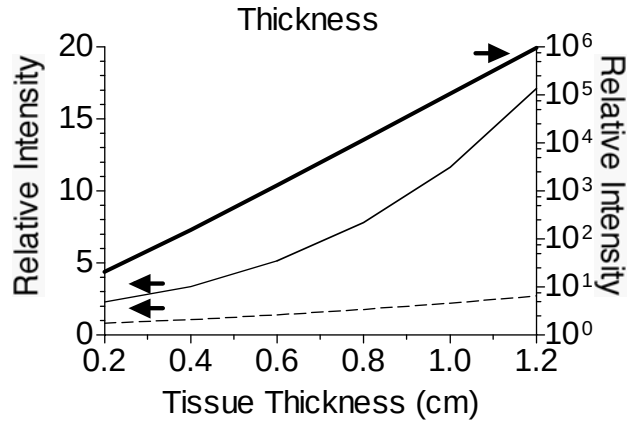
Wavelength-Independent Scatter





Wavelength-Dependent Scatter





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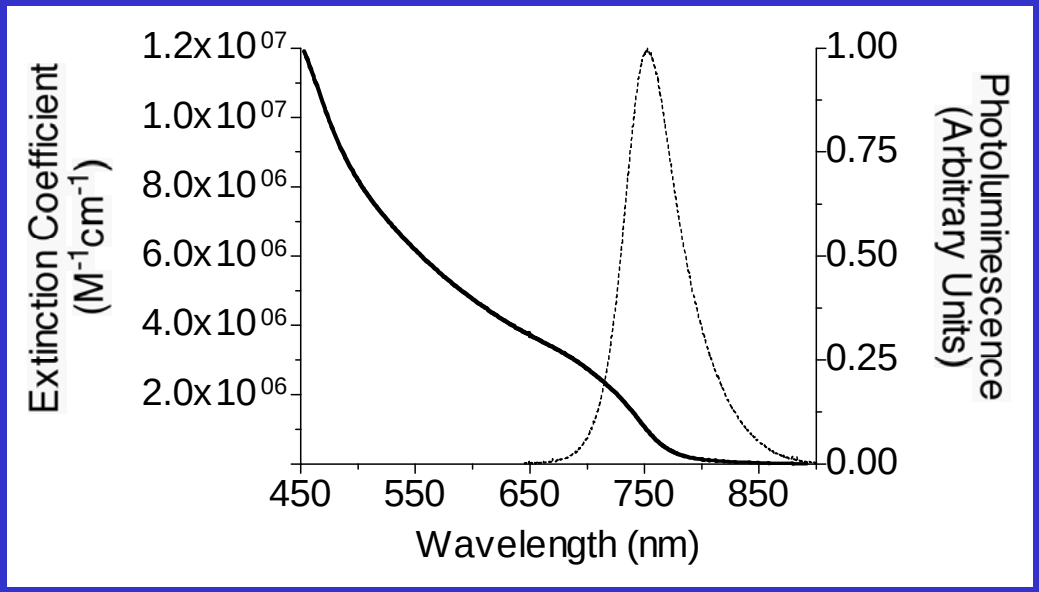
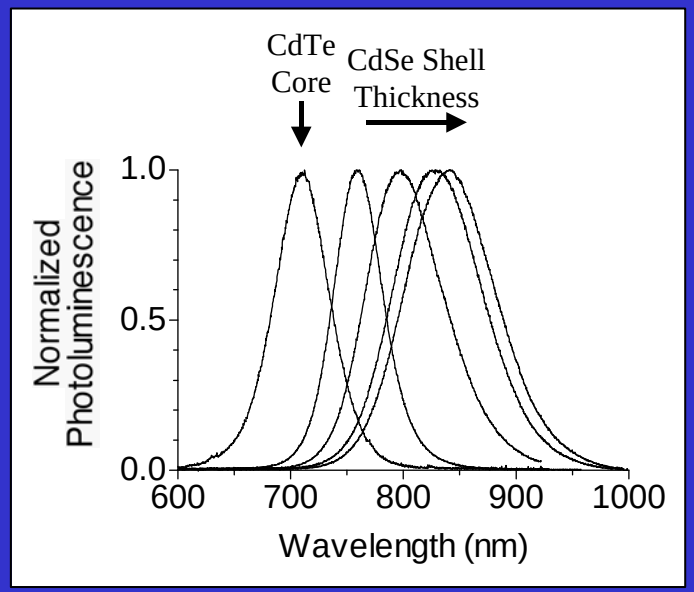
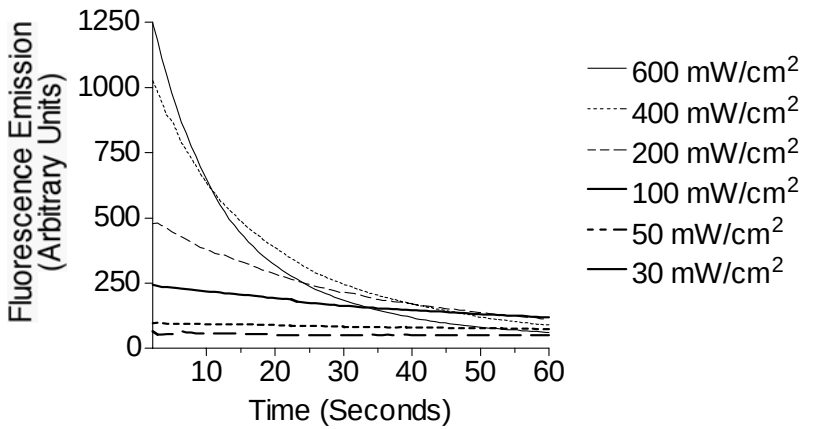
Near-Infrared Fluorescent (Quantum Dots)

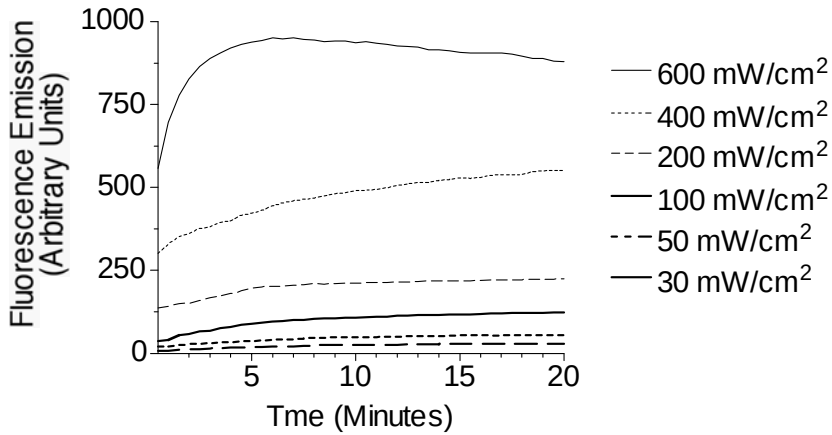




IRDye78-CA



NIR QDs

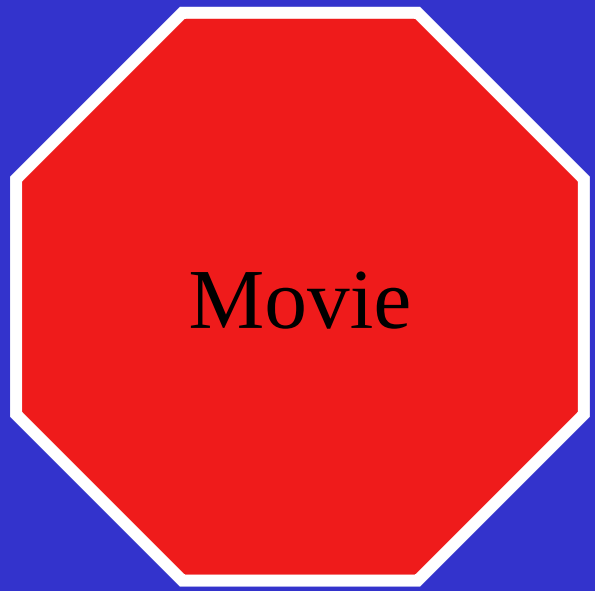


† Kim et al., Manuscript Submitted

Sentinel Lymph Node Mapping with 860 nm Quantum Dots
(15-20 nm hydrodynamic diameter)

Pig Femoral Lymph Node Model

200 µL of 2 µM Solution (400 pmol) of CdTe(CdSe)
QDs in PBS Injected Intradermally



Immediate Clinical Applications of NIR QDs

- Image guidance during sentinel lymph node mapping
- Image guidance during cancer resection
- Image guidance for avoidance of critical structures (e.g., nerves and blood vessels) during general surgery
- High sensitivity tool for surgical pathologists

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We have the clinical need.

NIBIB has funded the science.

We now have the nanotechnology solution.

But, can NIR and IR Fluorescent Quantum Dots ever be Translated to the Clinic?

Summary of Quantum Dots for *In Vivo* Applications

Reported Data

Type	Material	Molar Ratio	Emission Range(nm)	Hydrodynamic Diameter (nm)
I	CdSe	Cd:Se=1:1	480-650	2.6-9.8
I	CdTe	Cd:Te=1:1	580-740	4-12
II	CdTe(CdSe)	Cd:Te:Se=1:x:(1-x)	700-1100	4-16
I	InAs	In:As=1:1	800-1300	2-7
I	PbSe	Pb:Se=1:1	1100-2200	2.5-10
I	InP	In:P=1:1	600-730	2-5
I	HgS	Hg:S=1:1	500-800	1-5
I	CdHgTe	Cd:Hg:Se=x:(1-x):1	750-1100	6-12

Theoretical Data

Type	Material	Molar Ratio	Emission Range(nm)	Hydrodynamic Diameter (nm)
I	HgSe	Hg:Se=1:1	660-1600	4-6
I	HgTe	Hg:Te=1:1	660-1960	5-8
I	PbS	Pb:S=1:1	950-2060	4-8
I	PbTe	Pb:Te=1:1	780-2100	4-8
I	InSb	In:Sb=1:1	650-1330	8-12
I	GaAs	Ga:As=1:1	640-830	6-14
I	GaSb	Ga:Sb=1:1	800-1390	6-12
II	ZnTe(CdS)	Zn:Cd:Te:S=x:y:x:y	630-940	4-16
II	ZnTe(InAs)	Zn:In:Te:As=x:y:x:y	660-1000	4-16

Summary of QD Semiconductor Materials	Possible Routes of Administration
Antimonide	Intravenous
Arsenide	Intraperitoneal
Cadmium	Subcutaneous
Gallium	Subdermal
Indium	Intravaginal
Lead	PO
Mercury	Per-rectum
Phosphide	Intravesical
Selenide	Aerosol
Sulfide	
Telluride	
Zinc	

Unresolved Regulatory/Toxicity Issues

Will QDs be regulated as devices or drugs?

Will QDs be regulated based on their chemical form (i.e., salts), or as individual metals?

Does route of administration matter or do individual materials prevail?

Special design of toxicity studies?

Disposal of medical waste containing QDs

What We Need as Investigators

Guidance regarding “acceptable” materials or early indication that translation to the clinic is not possible

Assistance with the design and implementation of toxicity studies

Interagency cooperation regarding issues of drug delivery and disposal of QD-containing biological material

Acknowledgements (Presented Data)

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