

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

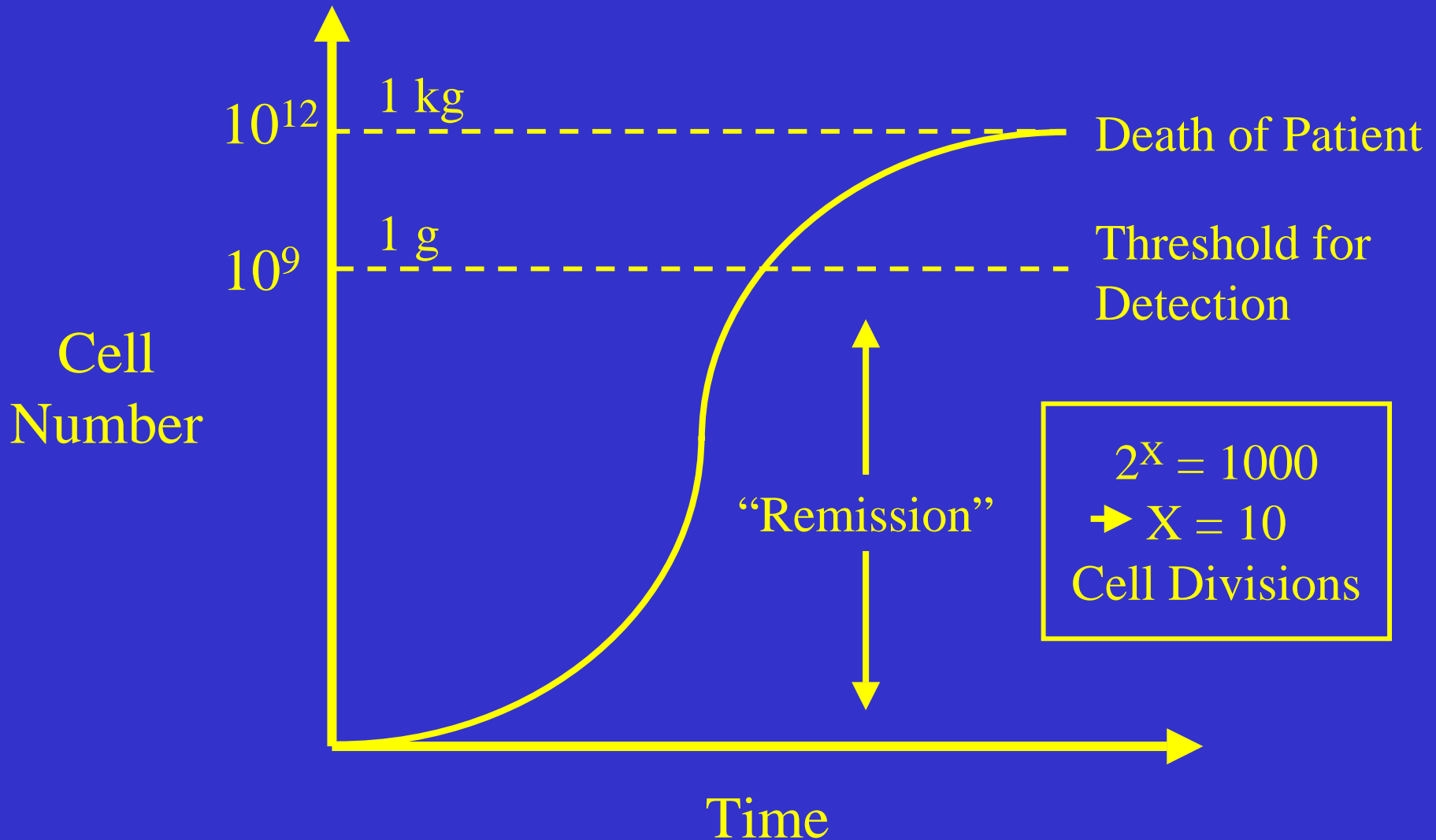
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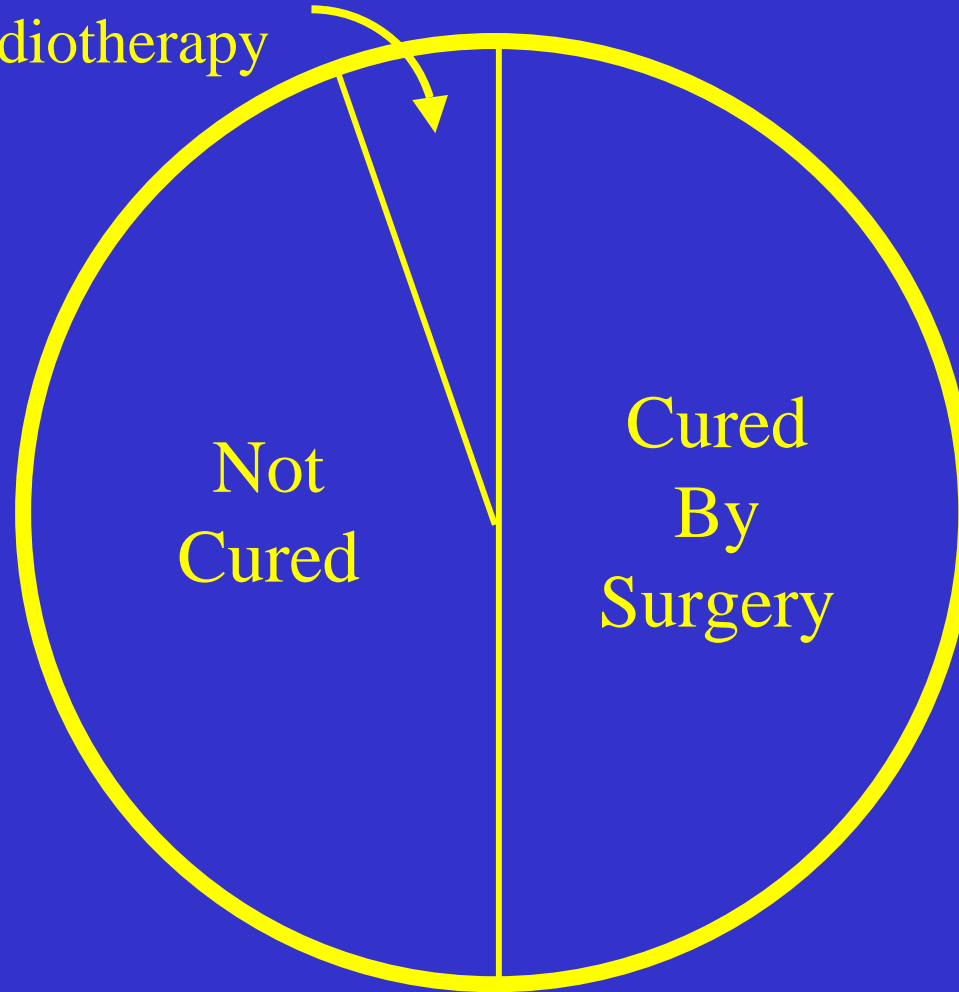
III. The Regulatory Conundrum

The Cancer Detection Problem



Cancer Fates in the United States

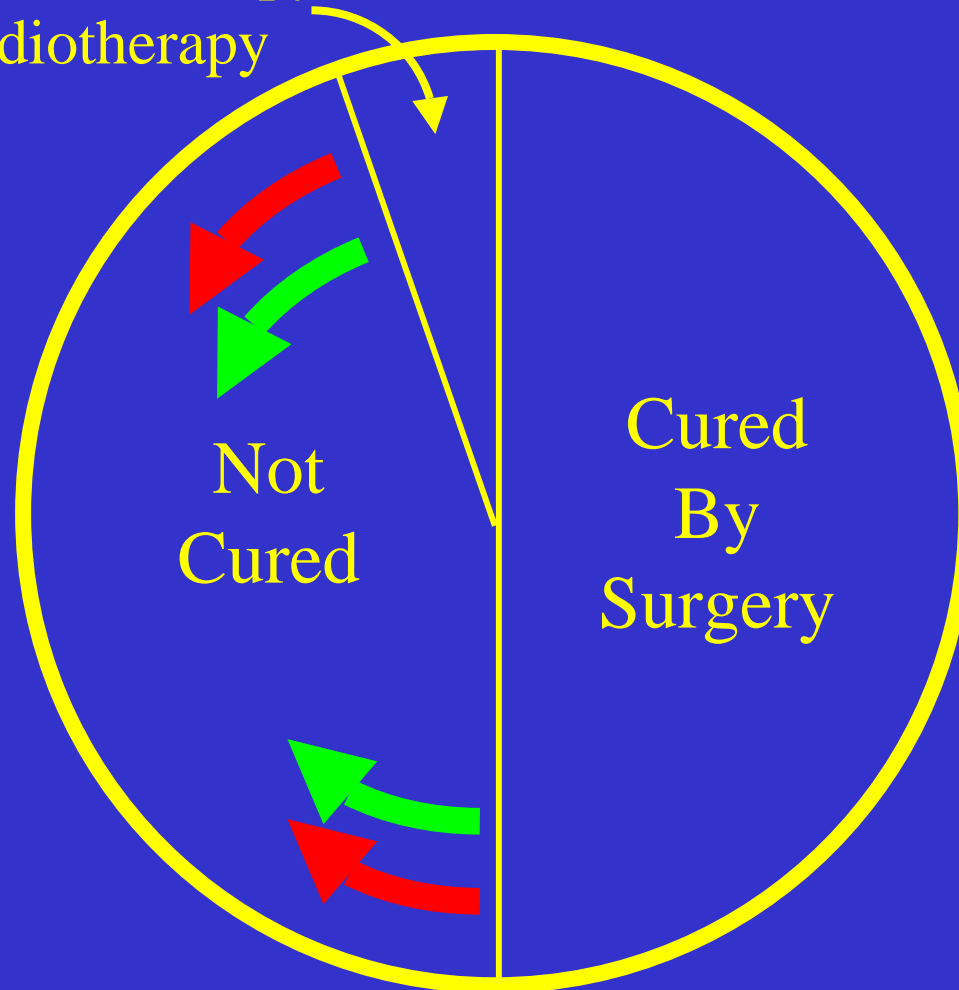
Cured by Chemotherapy and/or
Radiotherapy



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

Cancer Fates in the United States

Cured by Chemotherapy and/or
Radiotherapy



Chemistry (Molecular Targeting)
Engineering (Instrumentation)

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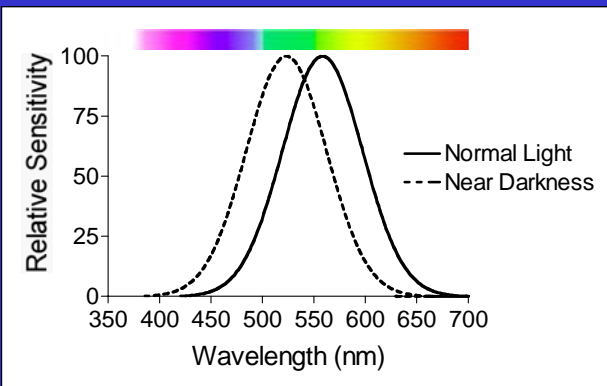
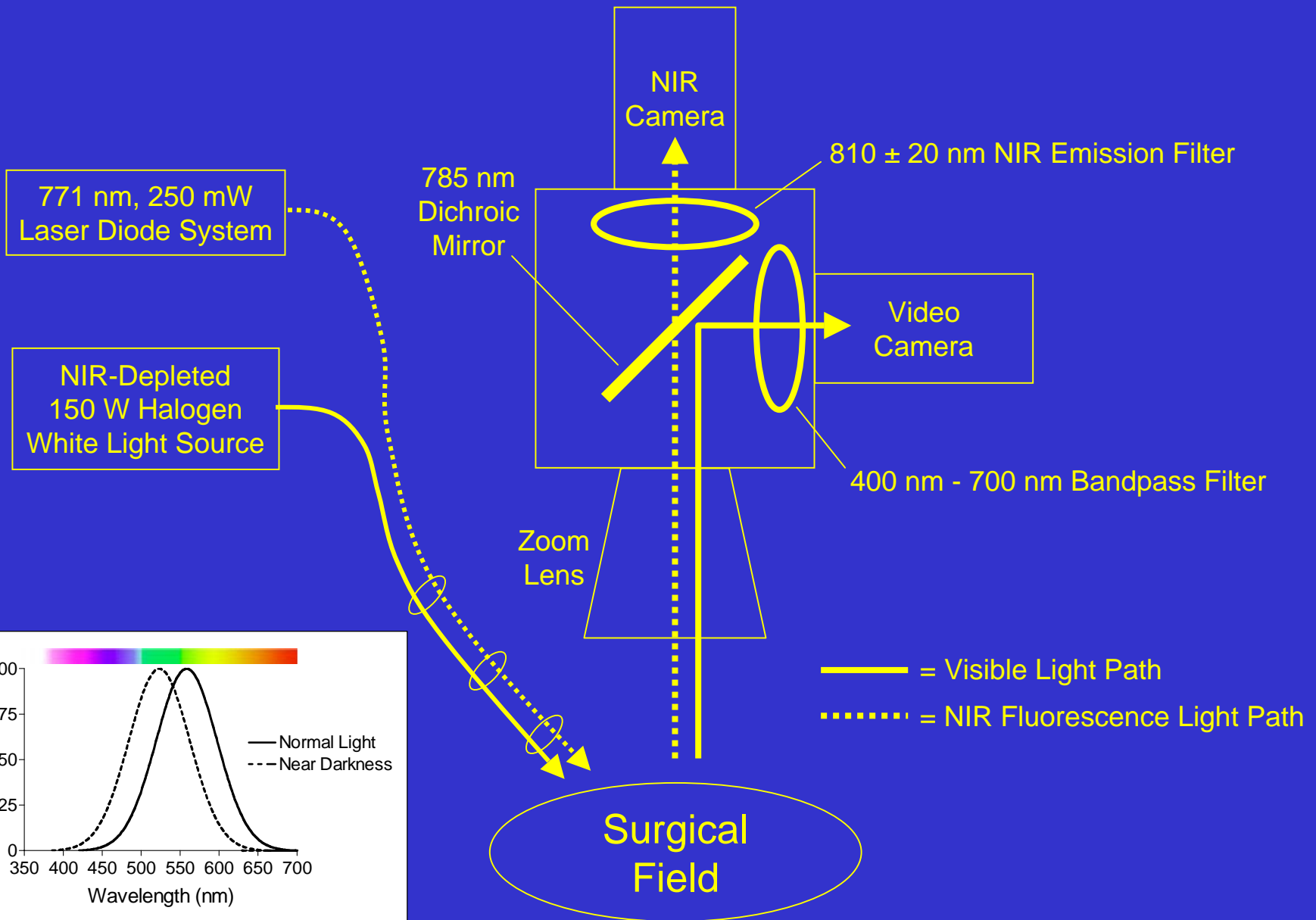
III. The Regulatory Conundrum

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

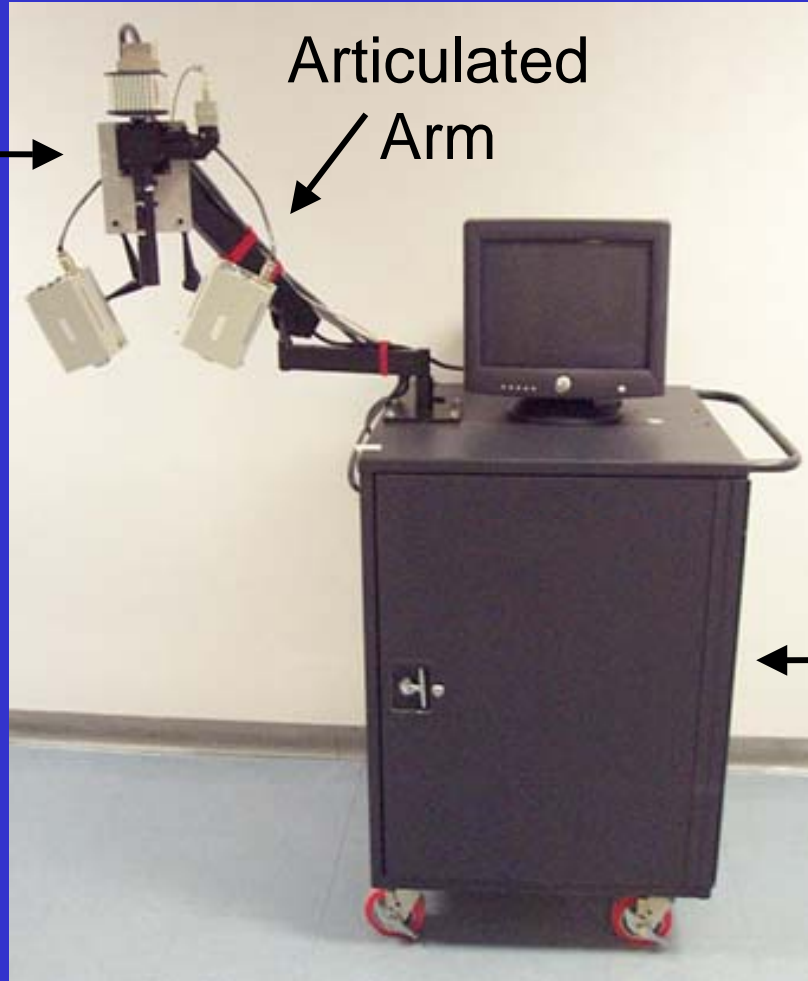


Mobile Large Animal Intraoperative Imaging System

Excitation/
Emission
Module



Articulated
Arm

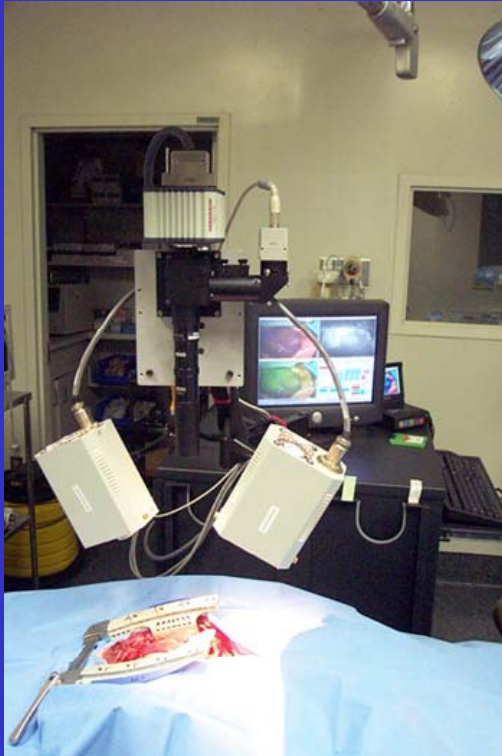


Computer &
Electronics
Cart



Deployment in the Surgical Suite

A.



B.



The Surgeon's View

The screenshot displays a medical imaging software interface with four main panels and a control panel on the right.

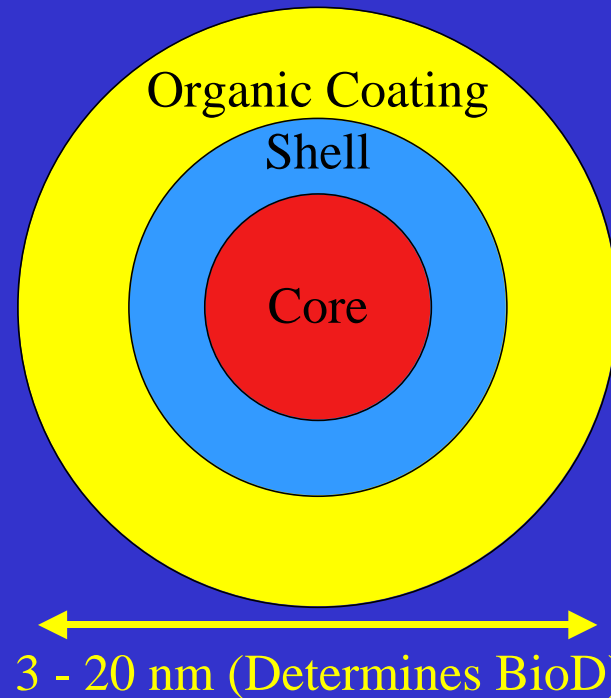
- Top-Left Panel:** A raw image window titled "legg1QD(13-29-43.03).C.tif136of177" showing a grayscale image of a patient's leg.
- Top-Right Panel:** A grayscale image window titled "legg1QD(13-29-43.03).N.tif136of177" showing a bright spot on the leg.
- Bottom-Left Panel:** A color-enhanced image window titled "legg1QD(13-29-43.03).M.tif136of177" showing the same leg with a green spot.
- Bottom-Right Panel:** A control panel titled "merge test5j.vi" with various settings and statistics.
 - NIR Test:** Includes a "Stop Acquire" button, a "Contrast Enhance Gain" slider (set to 255), and an "Exposure Time (msec; Default=60)" slider (set to 60).
 - DV Camera Selector:** Includes a "Hitachi Orca Merge" selector and a "Live Quantity" button.
 - Adjust Dynamic:** Includes an "Automatic" button and a "Pseudocolor" slider.
 - NIR Live Stats:** Includes a "Minimal Value" (123.00), "Maximal Value" (878.00), and "Mean Value" (205.98).
 - Brightness Contrast Gamma:** Includes three sliders for "Brightness" (100.0), "Contrast" (100), and "Gamma" (4.0).
 - Live ROI Statistics:** Includes a "Live Quantity" button and a table with "Min", "Max", and "Mean" values (all 0.00).
 - Snap ROI Statistics:** Includes a "Snap Quantity" button and a table with "Min", "Max", and "Mean" values (all 0.00).
 - Cine ROI Statistics:** Includes a "Cine Quantity" button and a table with "Min", "Max", and "Mean" values (all 0.00).
 - Buttons:** Includes "Snap Save (Footswitch #1)", "Snap Recall", "Cine Save (Footswitch #2)", "Cine Recall (Footswitch #3)", "Slideshow", "Snap Stop (Footswitch #1)", and "Cine STOP (Footswitch #1)".
 - Sliders:** Includes "Snap Index" (set to 0.00), "Time Lapse Delay (ms)" (set to 500), "ms per frame" (set to 125), and "Slideshow Index" (set to 136).

The Windows taskbar at the bottom shows the Start button, several application icons, and the system tray with the time "10:27 AM".

† DeGrand & Frangioni, Submitted

Fluorescent Semiconductor Nanocrystals (Quantum Dots)

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



Potential Advantages

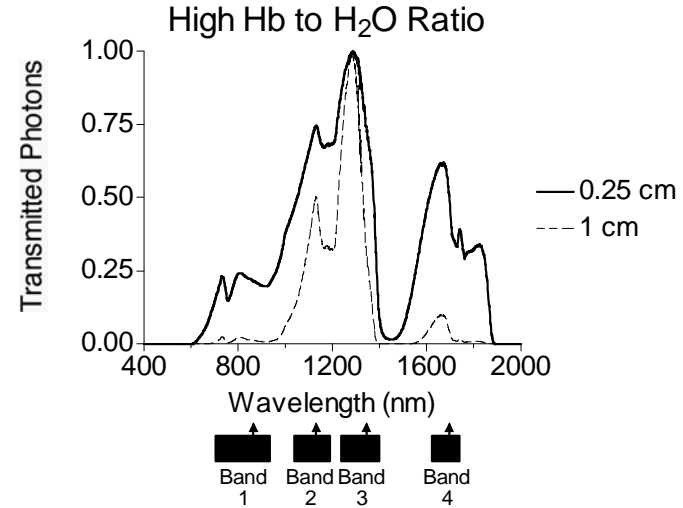
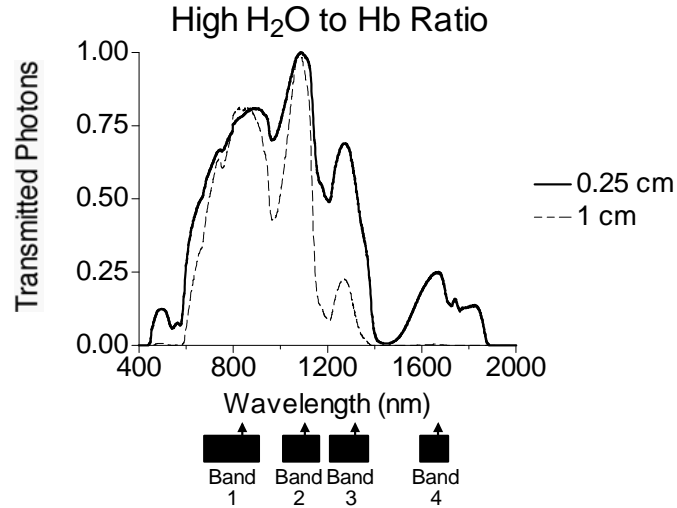
- Peak emission tunable anywhere from UV to IR
- High non-aqueous QYs
- Broadband absorption increasing to the blue
- High photostability
- Conjugatable to tumor targeting ligands

Potential Disadvantages

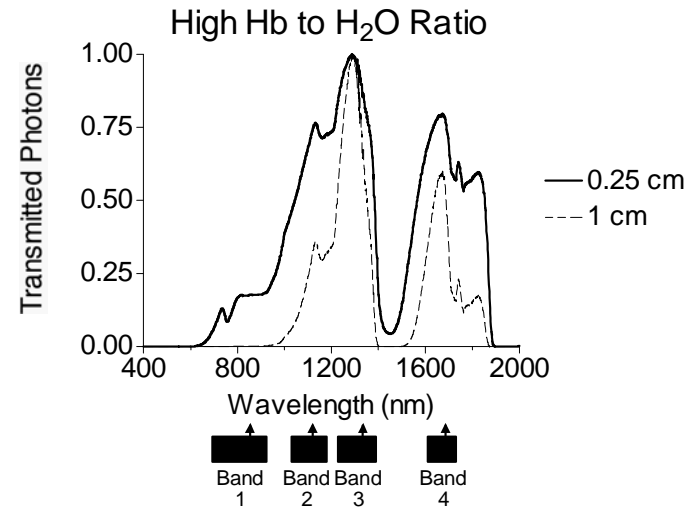
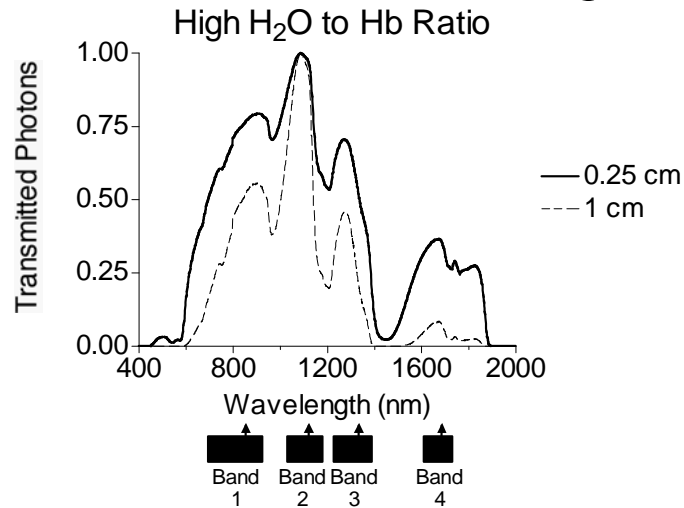
- Potential toxicity of materials
- Difficult to synthesize
- Size/material limitations (?solved)

Modeling of Near-Infrared and Infrared Photon Transmission

Wavelength-Independent Scatter



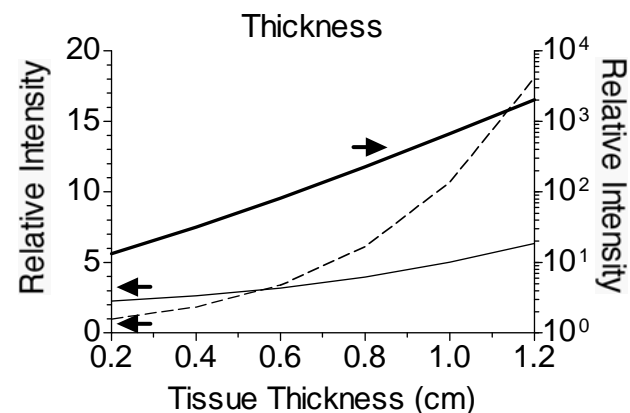
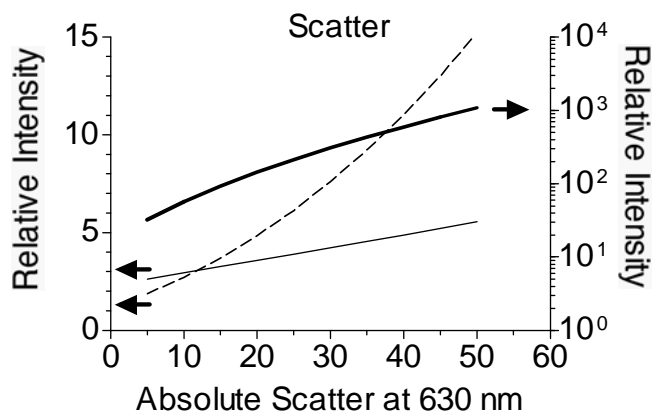
Wavelength-Dependent Scatter



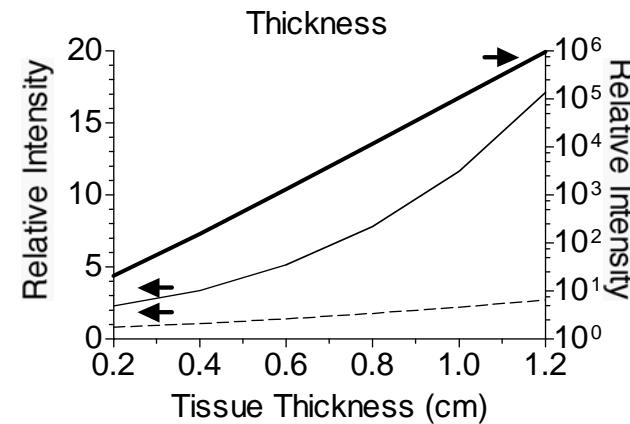
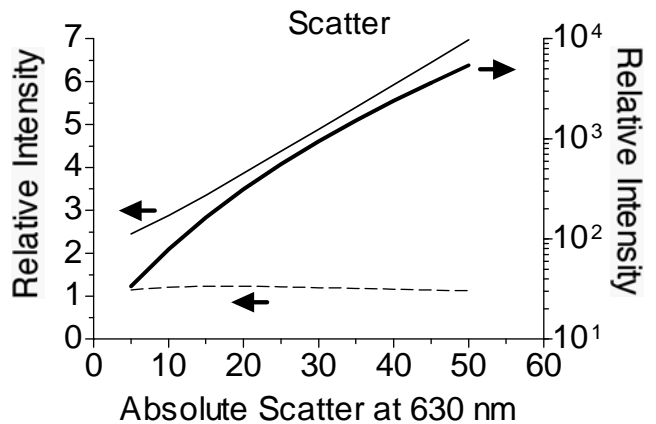
Infrared (1320 nm) QDs vs. NIR (840 nm) QDs

High Hb to H₂O Ratio

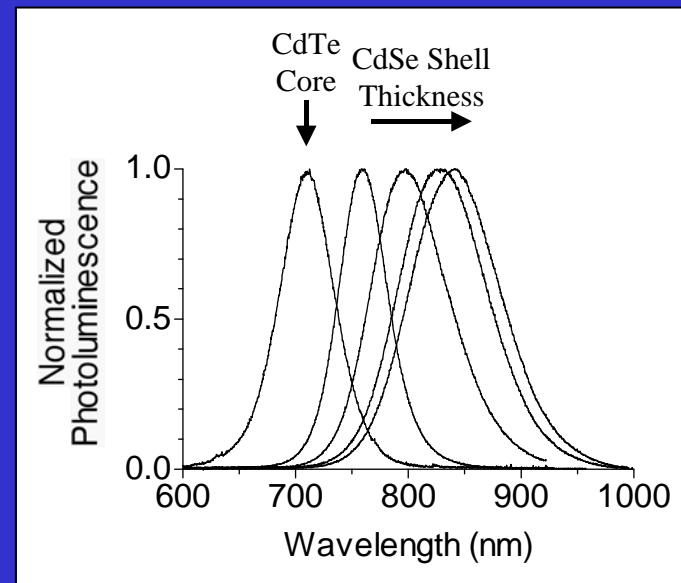
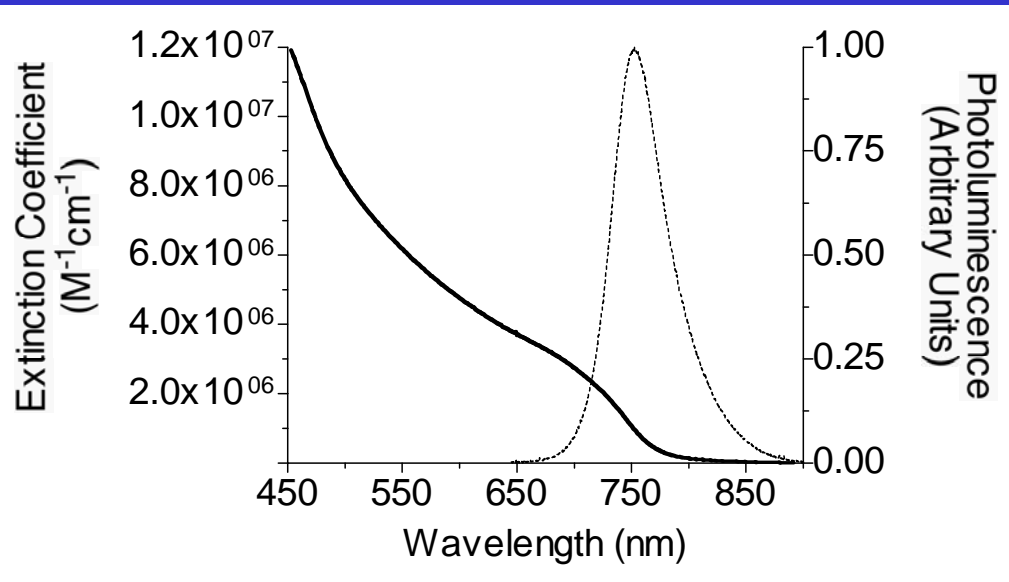
Wavelength-Independent Scatter



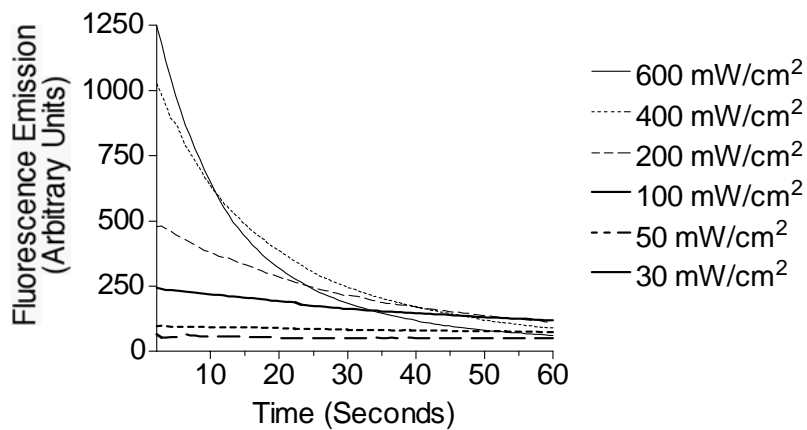
Wavelength-Dependent Scatter



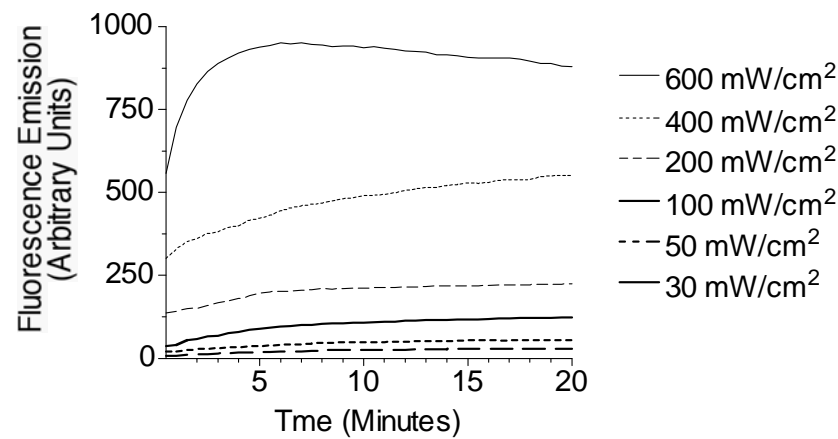
Near-Infrared Fluorescent (Quantum Dots)



IRDye78-CA



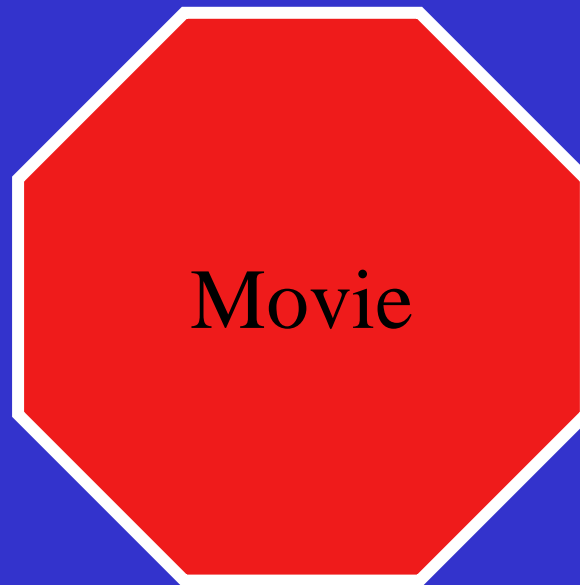
NIR QDs



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

<u>Type</u>	<u>Material</u>	<u>Molar Ratio</u>	<u>Emission Range(nm)</u>	<u>Hydrodynamic Diameter (nm)</u>
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

<u>Type</u>	<u>Material</u>	<u>Molar Ratio</u>	<u>Emission Range(nm)</u>	<u>Hydrodynamic Diameter (nm)</u>
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

Possible Routes of Administration

Materials

Antimonide

Arsenide

Cadmium

Gallium

Indium

Lead

Mercury

Phosphide

Selenide

Sulfide

Telluride

Zinc

Intravenous

Intraperitoneal

Subcutaneous

Subdermal

Intravaginal

PO

Per-rectum

Intravesical

Aerosol

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

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