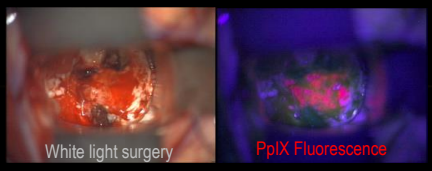
MOLECULAR IMAGING TO GUIDE SURGERY & RADIOTHERAPY



Brian W Pogue, Ph.D.
Thayer School of Engineering, Geisel School of Medicine
Dept. of Physics & Astronomy, Dartmouth College

DISCLOSURE

Brian Pogue is Co-Founder & President of DoseOptics LLC, developing a commercial prototype of Čerenkov imaging for radiation therapy delivery verification.

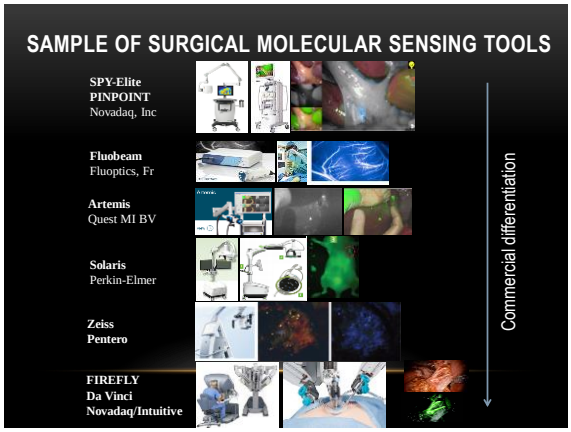
OUTLINE

Macroscopic tools for fluorescence molecular-guided surgery

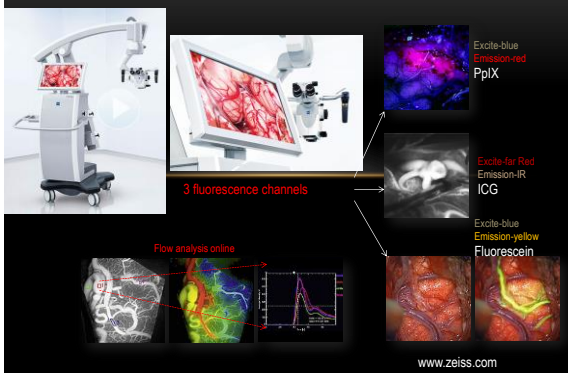
Problems & solutions

- #1 - wide dynamic range needs
- #2 – room light issues
- #3 - vascular delivery dominating signals
- #4 – deeper optical imaging through more than 1cm is hard

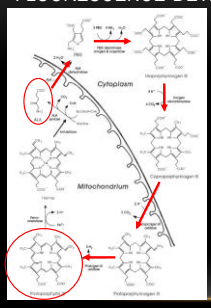
SAMPLE OF SURGICAL MOLECULAR SENSING TOOLS

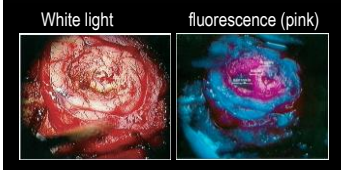


Zeiss Pentero 900 Neurosurgical Station



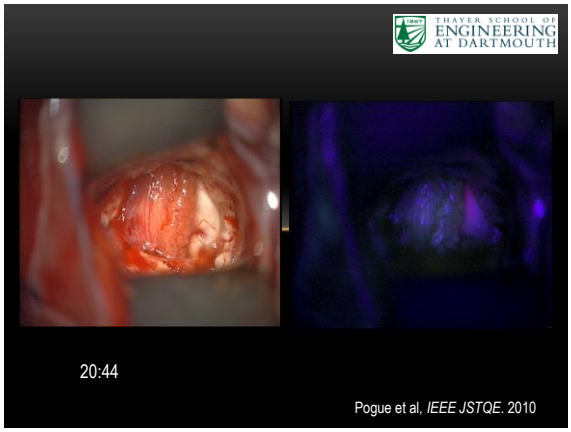
AMINOLEVULINIC ACID-PROTOPORPHYRIN IX FLUORESCENCE DETECTION





FRIESEN, ET AL. INTERNATIONAL JOURNAL OF ONCOLOGY, 21: 577-582, 2002.

Stummer et al, J. Neurosurg, 2000
Stummer et al, Lancet Oncol. 2006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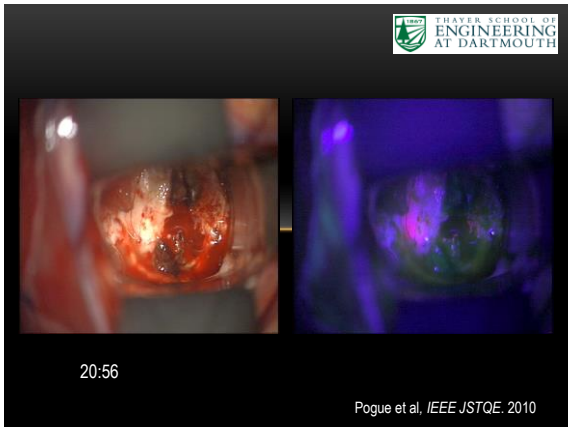
AT DARTMOUTH
20:44
Pogue et al, *IEEE JSTQE*. 2010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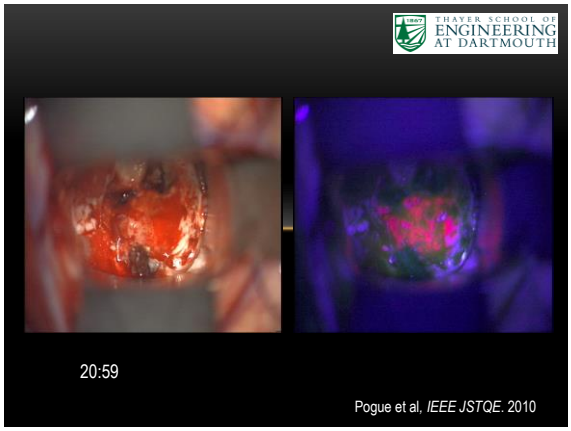
Pogue et al, *IEEE JSTQE*. 2010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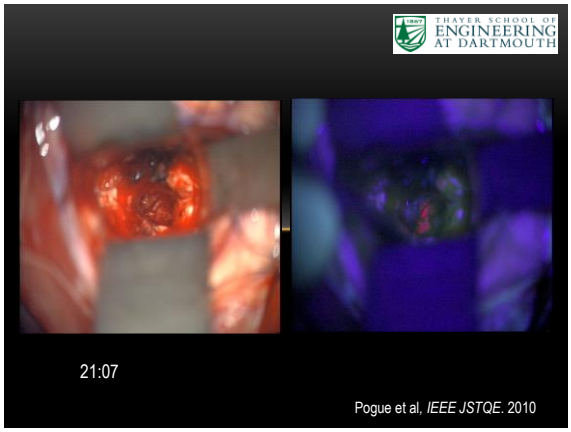
Pogue et al, *IEEE JSTQE*. 2010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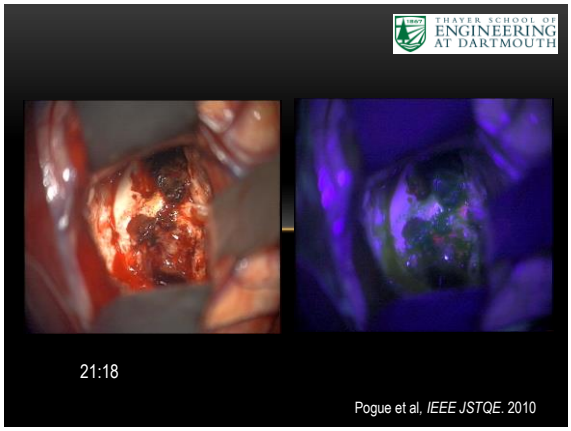
Pogue et al, *IEEE JSTQE*. 2010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AT DARTMOUTH
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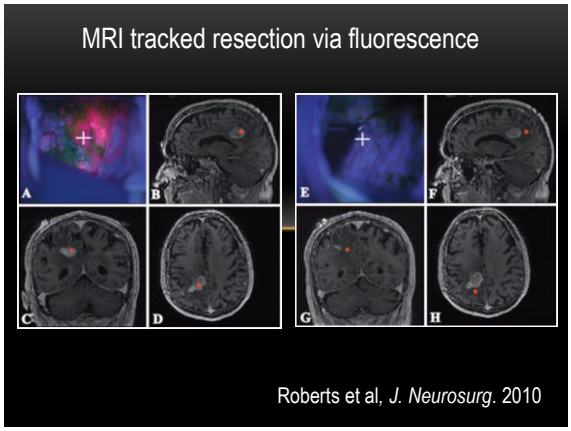
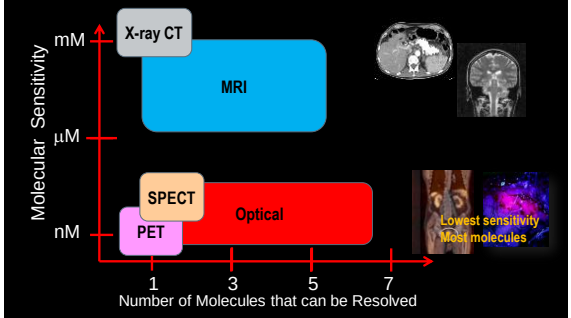
Pogue et al, *IEEE JSTQE*. 2010

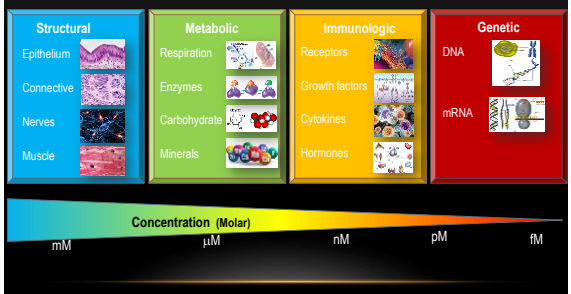

MRI tracked resection via fluorescence
A
B
C
D
E
F
G
H
Roberts et al, *J. Neurosurg*. 2010

WHAT ARE THE STRENGTHS OF OPTICAL MOLECULAR IMAGING ?

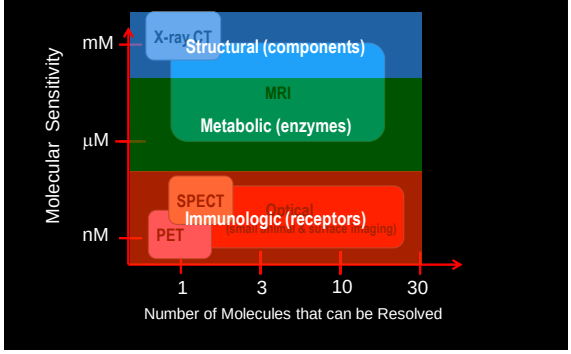


Pogue et al, Am J. Roentgen. 2010

POSSIBLE MOLECULAR DETECTION FEATURES



SENSITIVITY & SPECIFICITY ARE KEY



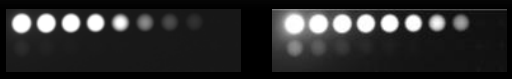
Problem # 1

Increasing dynamic range usability

IMAGING AT 8-BITS VS 12, 14, 16 BITS

Original + Window-Level

$Log_{1.06}$(Original) + Window-Level



Observations:
Wider dynamic range is visualized
Can be applied in real time
Crosstalk between high-low regions better visualized

$$2^8 = \log_x(2^N - b)$$

b = background, x= compression ratio

LYMPHATIC TRACKING IN RAT MODEL

(VIEWED BY LI-COR PEARL IMAGER AT 24 –BIT DYNAMIC RANGE)

Original + Window-Level

$Log_{1.06}$(Original) + Window-Level

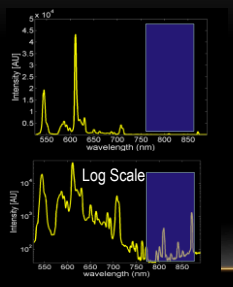
This allows real time visualization of entire dynamic range for surgery

DSouza et al, J. Biomed. Opt. (in press, 2015)

Problem #2

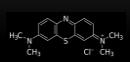
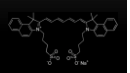
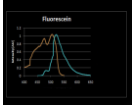
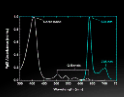
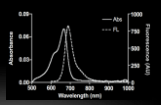
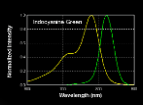
Imaging fluorescence with room lights on

ROOM LIGHTS & FLUORESCENCE GUIDED SURGERY

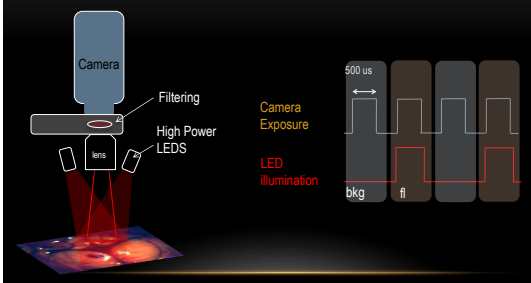


Novodaq – FDA approved for ICG imaging

CLINICALLY APPROVED FLUORESCENT DYES

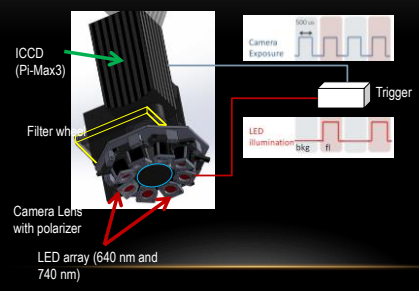
Fluorescein	Protoporphyrin IX	Methylene Blue	Indocyanine Green
			
Blue green	Blue/red Red-NIR	Red NIR	NIR NIR
			

IMAGING WITH PULSED-LIGHT/GATED DETECTION:



Sexton et al, Optics Letters, 2013

PULSED IMAGING SYSTEM HARDWARE



Sexton et al, Optics Letters, 2013

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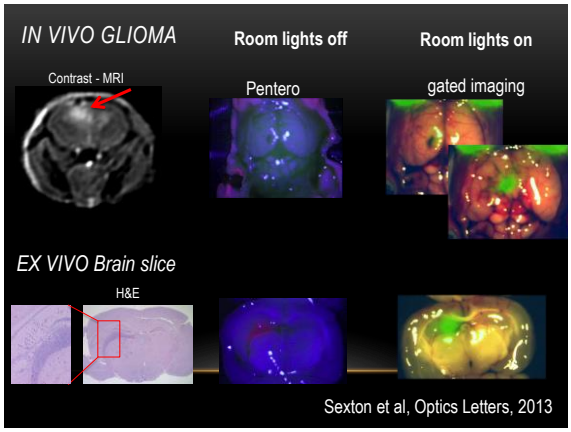
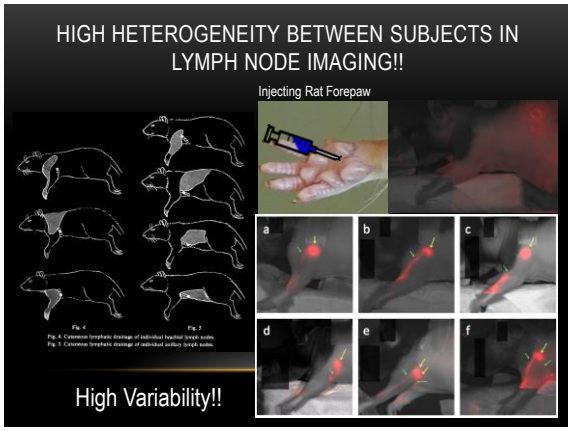
Sexton et al, Optics Letters, 2013



Problem #3

Contrast agent delivery is dominated by permeability not molecular binding,

so the raw signal is not purely molecular imaging

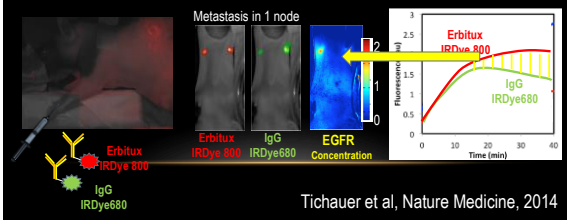


RATIOMETRIC IMAGING IS MUCH MORE ACCURATE….

nature medicine

Microscopic lymph node tumor burden quantified by macroscopic dual-tracer molecular imaging

Kenneth M Tichauer[1], Kimberley S Samkoe[2], Jason R Gunn[3], Stephen C Kanick[3], P Jack Hoopes[2,3], Richard J Barth[2], Peter A Kaufman[4], Tayyaba Hasan[5] & Brian W Pogue[2,3,5]



Tichauer et al, Nature Medicine, 2014

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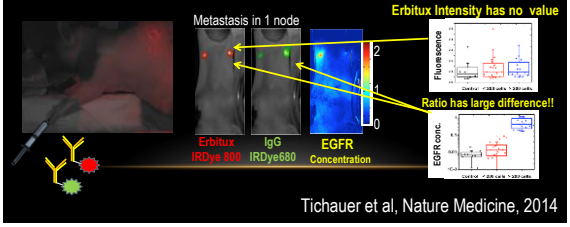

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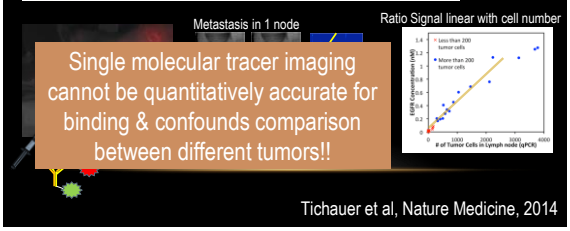
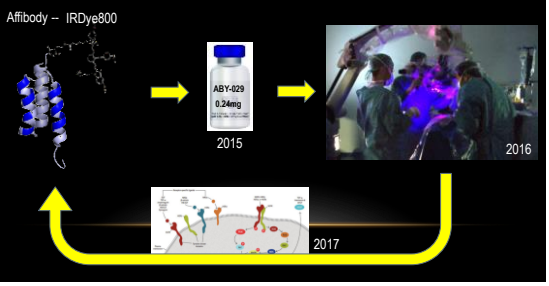


Tichauer et al, Nature Medicine, 2014

Industry/Academic Partnership for Targeted Fluorescent Receptor probe

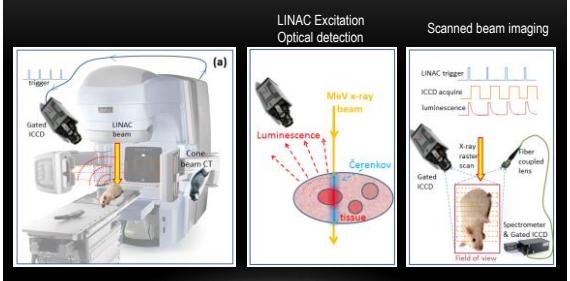
Affibody AB – LI-COR – Dartmouth



Problem #4

Imaging deeper with light is hard

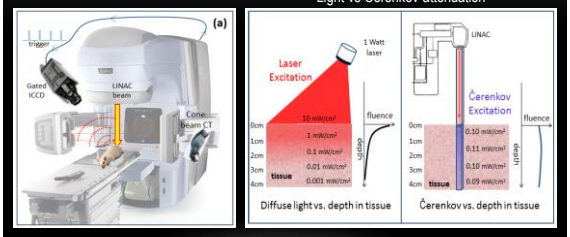
Cerenkov-excited luminescence imaging



Zhang et al, Optics Letters 2015

Cerenkov-excited luminescence imaging

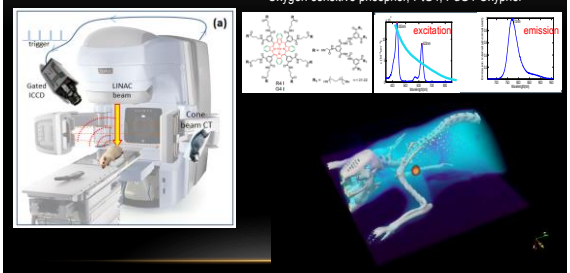
Light vs Cerenkov attenuation



Zhang et al, Optics Letters 2015

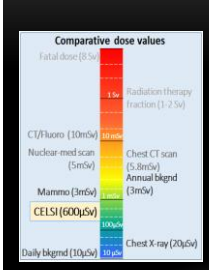
Cerenkov-excited luminescence imaging

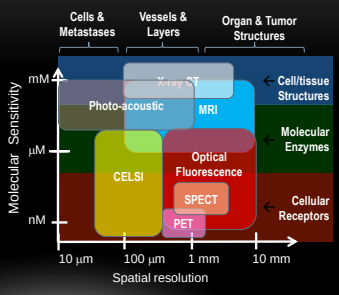
Oxygen sensitive phosphor, PtG4, PdG4 Oxyphor



Zhang et al, Optics Letters 2015

Cerenkov-excited luminescence imaging





Zhang et al, Optics Letters 2015

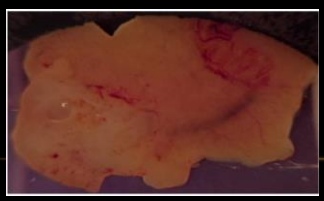
SUMMARY

1. **Molecular guided surgery** is now a reality in oncology.
2. **Log-compression** video display allows wider dynamic range fluorescence video (just as it is for ultrasound).
3. **Gated imaging** eliminates room interference (for visible fluorophores)
4. **Contrast agent cocktails** which provide more information could improve things.
5. **Čerenkov molecular imaging** allows optical imaging through several centimeters of tissue.

Optics in Medicine @ Dartmouth

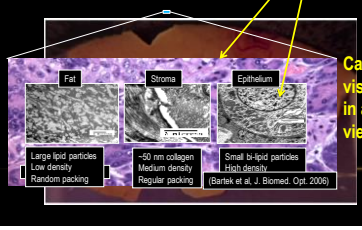
Example #2

Enhancing scatter/structure contrast



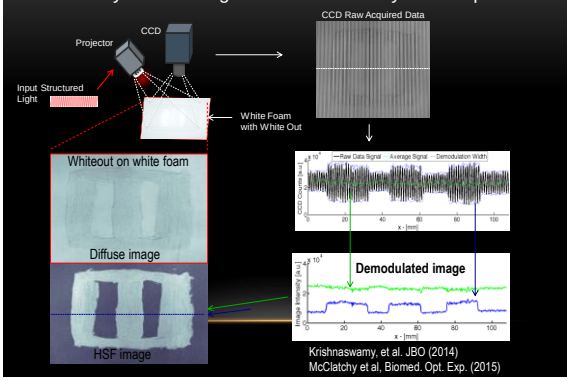
Surgical margin detection on excised specimens

Macroscopic: Scatter
Microscopic: cellular/matrix
Ultrastructure: fibrils, organelles, vesicles



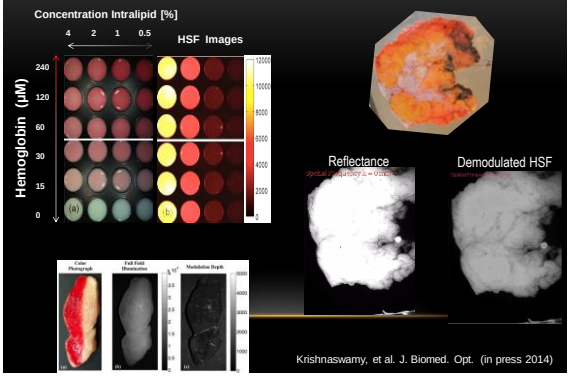
Can this be visualized rapidly, in a wide field of view (ie. surgery)?

High Spatial Frequency (HSF) Structured Light increases sensitivity to scattering and limits sensitivity to absorption



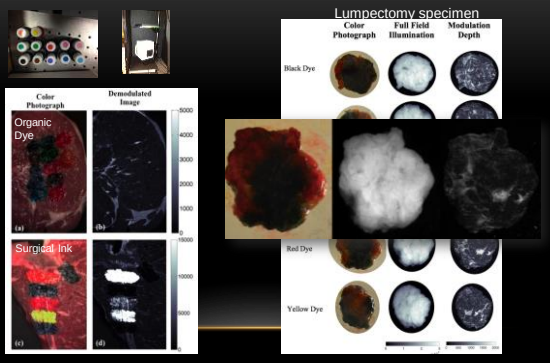
Krishnaswamy, et al. JBO (2014)
McClatchy et al, Biomed. Opt. Exp. (2015)

HSF REMOVES THE EFFECT OF ABSORPTION!!



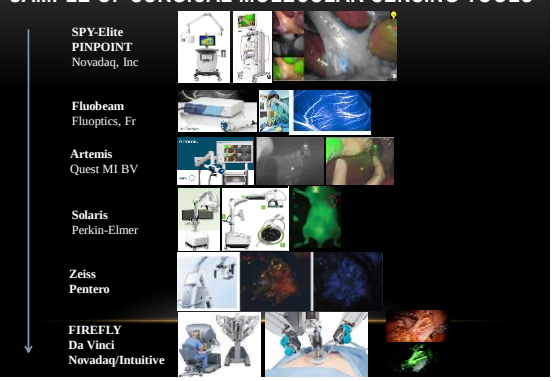
Krishnaswamy, et al. J. Biomed. Opt. (in press 2014)

INSENSITIVITY TO ORGANIC DYE ABSORPTION



McClatchy, et al. J. Biomed. Opt. (2015)

SAMPLE OF SURGICAL MOLECULAR SENSING TOOLS



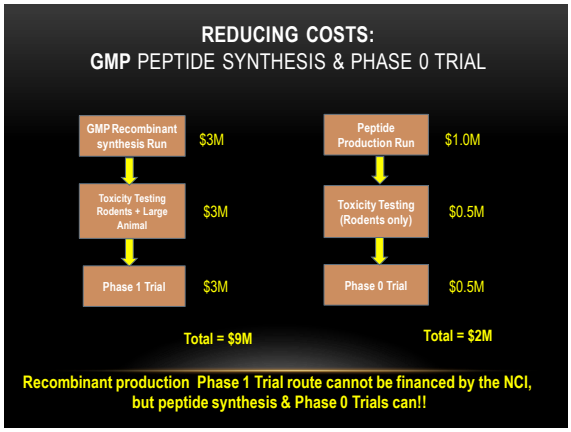
PROBLEM #4: FINANCIAL BARRIERS TO MOLECULAR IMAGING

Lack of existing paradigm for molecular guided surgery = NO BILLING CODE

Modest financial payback for diagnostics (vs. therapeutics)

The Cost of Developing Imaging Agents for Routine Clinical Use

able for the development costs of therapeutic drugs. The cost of developing a drug for diagnostic imaging to commercialization is in the $100 to $200 million range, whereas a blockbuster imaging drug has current sales of $200 to $400 million. Most of these blockbuster


REDUCING COSTS:
GMP PEPTIDE SYNTHESIS & PHASE 0 TRIAL
GMP Recombinant synthesis Run
$3M
Toxicity Testing Rodents + Large Animal
$3M
Phase 1 Trial
$3M
Total = $9M
Peptide Production Run
$1.0M
Toxicity Testing (Rodents only)
$0.5M
Phase 0 Trial
$0.5M
Total = $2M
Recombinant production Phase 1 Trial route cannot be financed by the NCI, but peptide synthesis & Phase 0 Trials can!!