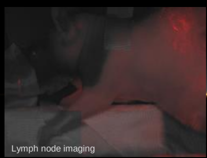
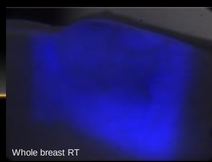
OPTICAL IMAGING IN BREAST CANCER:

FLUORESCENCE & ČERENKOV





Brian W. Pogue PhD

Outline

1. Dual-probe fluorescence imaging for lymph node cancer detection
2. Cerenkov Imaging in Radiation Therapy
3. Hybrid Molecular imaging

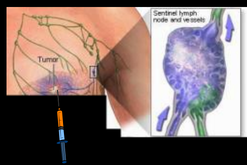
Example 1: Detecting lymph node involvement

with

Exogenous molecular imaging

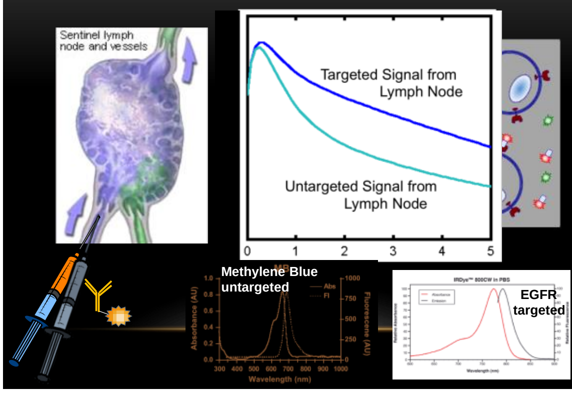
LYMPH NODE DETECTION

Lymphoscintigraphy **Methylene Blue procedure**



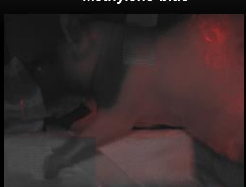
1) Procedures today remove nodes for the purpose of ass
2) Delay between surgery and lymph node analysis
3) High morbidity (axillary nodes)

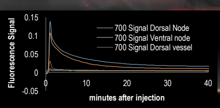
Dual Dye injection: Targeted & Reference

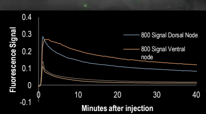


EPIDERMAL GROWTH FACTOR RECEPTOR TARGETED FLUORESCENT IMAGING

Methylene blue **EGFR binding peptide + IRDye800**



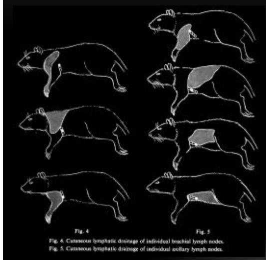




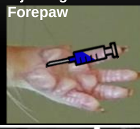
Alisha DSouza

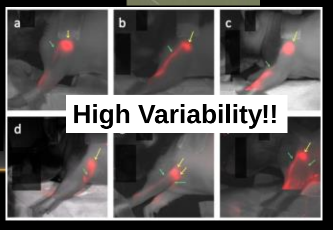
Courtesy: Alisha D'Souza

FLUORESCENCE IMAGING OF AXILLARY LYMPH NODES



Injecting Rat Forepaw

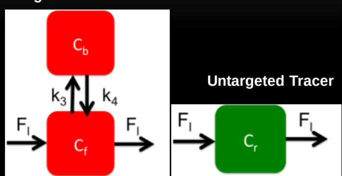


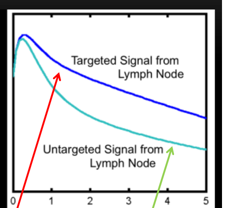


DUAL REPORTER COMPARTMENT MODEL

Targeted Tracer

Untargeted Tracer





$$\frac{dC_f}{dt} = F_l C_l - (F_l + k_3)C_f + k_4 C_b \qquad \frac{dC_r}{dt} = F_l C_l - F_l C_r$$

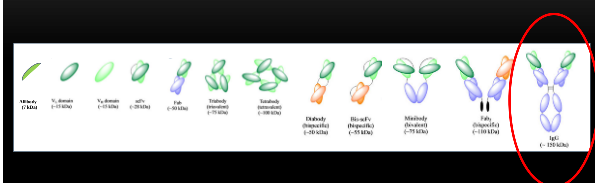
$$\frac{dC_b}{dt} = k_3 C_f - k_4 C_b \qquad \boxed{BP = k_3/k_4}$$

$$C(t) = C(t) + F_l C(t) * e^{-\frac{F_l}{1+BP}t}$$

Tichauer et al., *Phys Med Biol 2012*

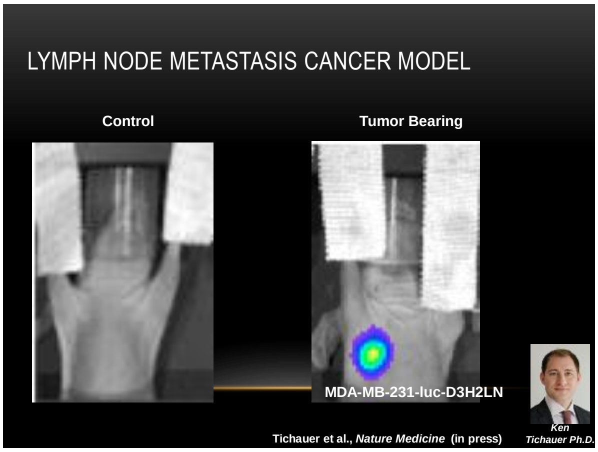
8

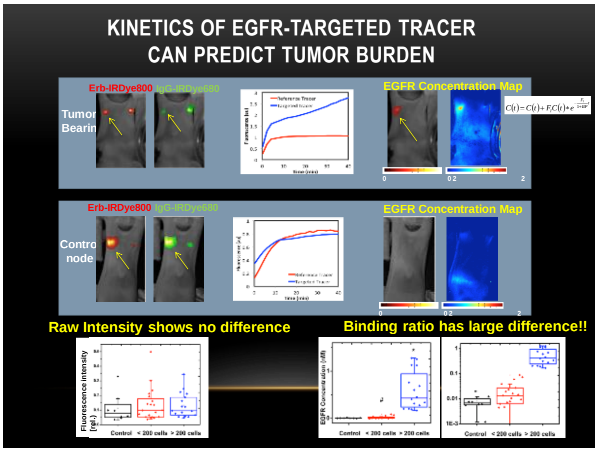
SIZE → AFFINITY – TRANSPORT EFFECTS

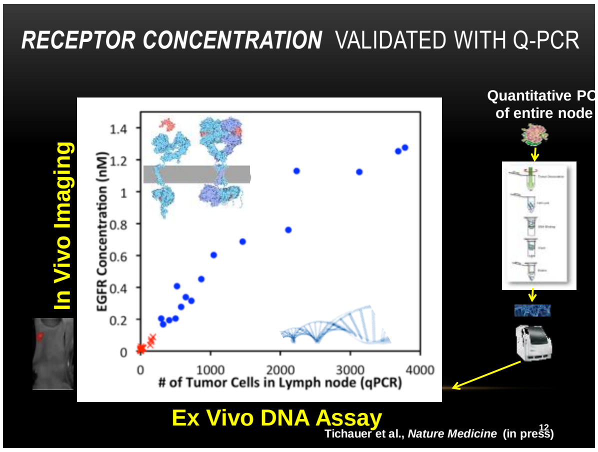


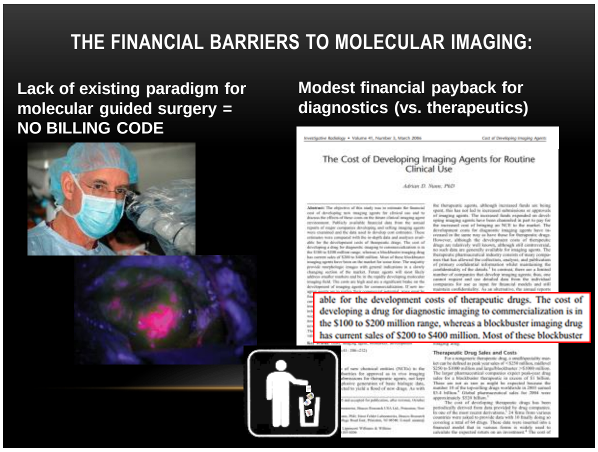
Shorter clearance time ↔ Longer clearance time
Lower affinity ↔ Higher affinity

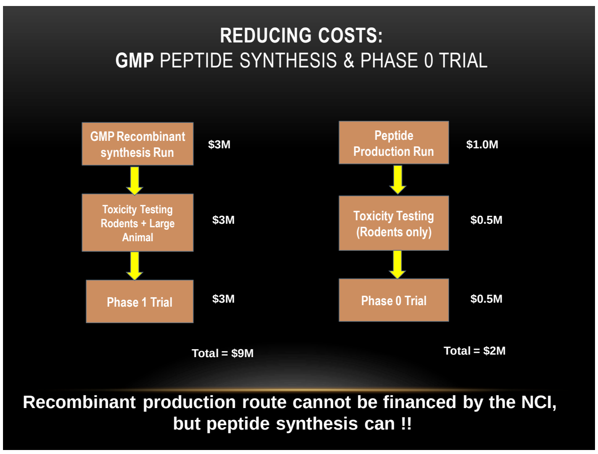
9

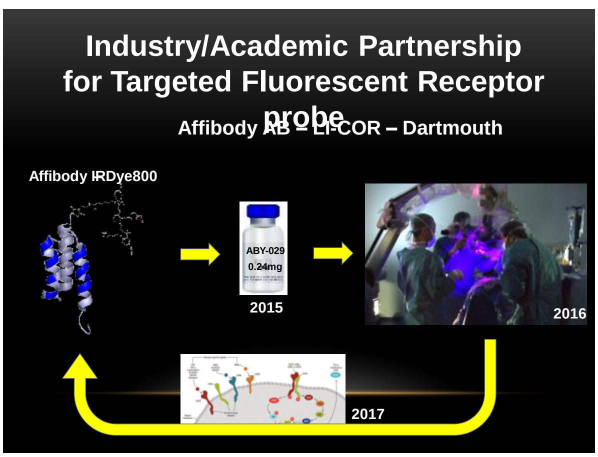

LYMPH NODE METASTASIS CANCER MODEL
Control
Tumor Bearing
MDA-MB-231-luc-D3H2LN
Tichauer et al., Nature Medicine (in press)
Ken Tichauer Ph.D.


KINETICS OF EGFR-TARGETED TRACER CAN PREDICT TUMOR BURDEN
Erb-IRDye800
IgG-IRDye680
Tumor Bearin
EGFR Concentration Map
Erb-IRDye800
IgG-IRDye680
Contro node
EGFR Concentration Map
Raw Intensity shows no difference
Binding ratio has large difference!!
Control
< 200 cells
> 200 cells


RECEPTOR CONCENTRATION VALIDATED WITH Q-PCR
In Vivo Imaging
EGFR Concentration (nM)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
1000
2000
3000
4000
# of Tumor Cells in Lymph node (qPCR)
Quantitative PC
of entire node
Ex Vivo DNA Assay
Tichauer et al., Nature Medicine (in press)
12

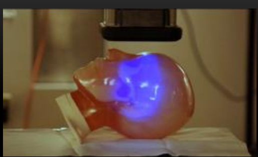

THE FINANCIAL BARRIERS TO MOLECULAR IMAGING:
Lack of existing paradigm for molecular guided surgery = NO BILLING CODE
Modest financial payback for diagnostics (vs. therapeutics)
The Cost of Developing Imaging Agents for Routine Clinical Use
able for the development costs of therapeutic drugs. The cost 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

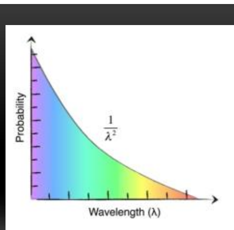

REDUCING COSTS:
GMP PEPTIDE SYNTHESIS & PHASE 0 TRIAL
GMP Recombinant synthesis Run
$3M
Toxicity Testing Rodents + Large Animal
$3M
Phase 1 Trial
$3M
Total = $9M
Peptide Production Run
$1.0M
Toxicity Testing (Rodents only)
$0.5M
Phase 0 Trial
$0.5M
Total = $2M
Recombinant production route cannot be financed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


Industry/Academic Partnership for Targeted Fluorescent Receptor probe
Affibody AB – LI-COR – Dartmouth
Affibody IRDye800
ABY-029
0.24mg
2015
2016
2017

Cerenkov Imaging in Radiation Therapy

The Čerenkov effect





Dose deposition

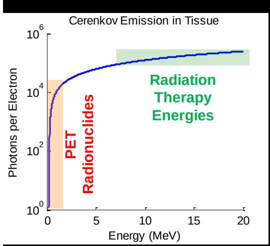
$$D = \frac{1}{\rho}\int \Phi\left(\frac{-dT}{dx}\right) dE$$

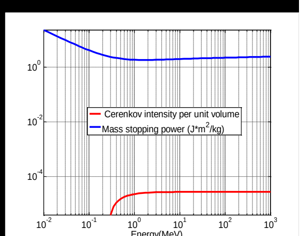
Čerenkov production

$$N = \frac{1}{\rho}\int \Phi\left(\frac{dN}{dx}\right) dE$$

Cherenkov radiation and its applications, Jelley Glaser, *et. al.*, Med. Phys. (2013)

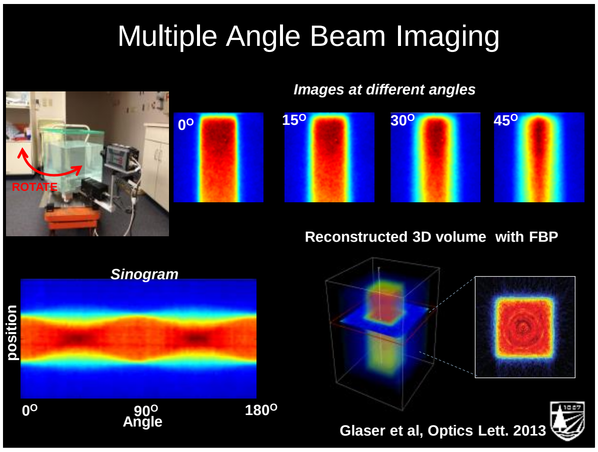
Čerenkov emission, energy & dose

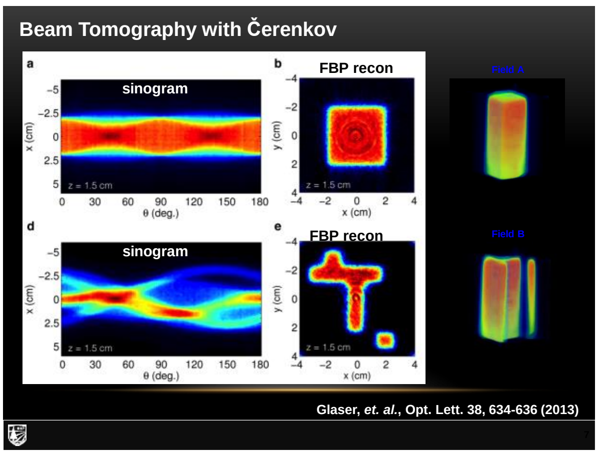


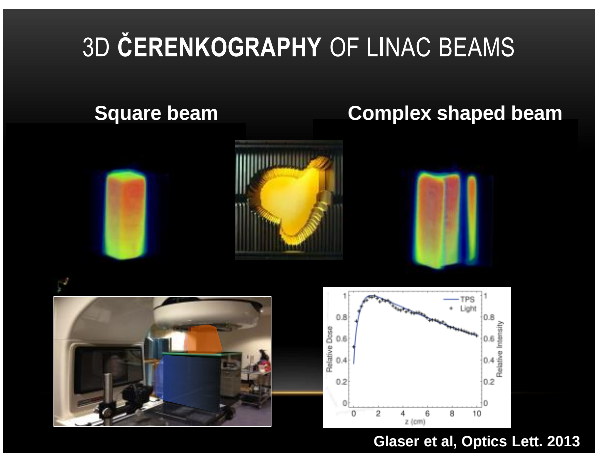


High production of Cerenkov in EBRT relative to PET or brachytherapy

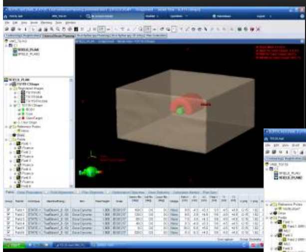
Production is largely flat with energy > 1 MeV


Multiple Angle Beam Imaging
Images at different angles
ROTATE
0°
15°
30°
45°
Reconstructed 3D volume with FBP
Sinogram
position
0°
90°
Angle
180°
Glaser et al, Optics Lett. 2013

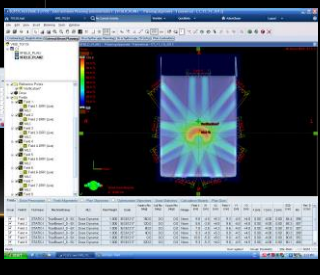

Beam Tomography with Čerenkov
a
sinogram
x (cm)
z = 1.5 cm
θ (deg.)
b
FBP recon
y (cm)
x (cm)
d
sinogram
e
FBP recon
Glaser, et. al., Opt. Lett. 38, 634-636 (2013)


3D ČERENKOGRAPHY OF LINAC BEAMS
Square beam
Complex shaped beam
TPS
Light
Relative Dose
Relative Intensity
z (cm)
Glaser et al, Optics Lett. 2013

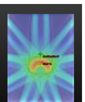
Imaging Complex Treatment plans in real time



AAPM TG Report # 119

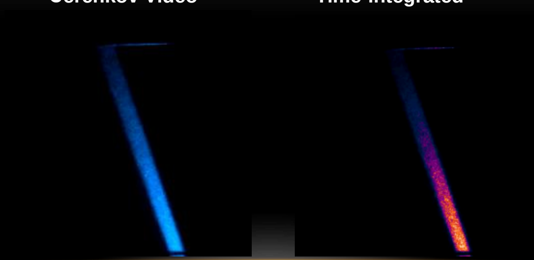


IMRT C-shape Plan in real time



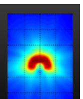
Čerenkov Video

Time-integrated



Glaser et al, Med. Phys. (2014)

VMAT Plan in real time



Čerenkov Video

Time-integrated

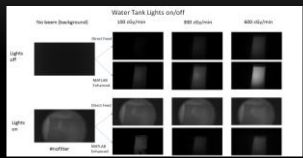
David Gladstone, Thursday presentation AAPM

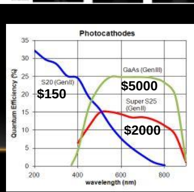
Optical dosimetry system v3.0 Low Cost option
($250 in parts)

Web cam $50

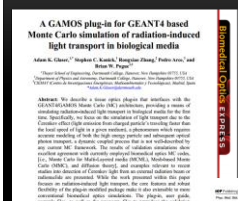
Nightvision monocular $150

filter $50





MONTE CARLO MODELING – GEANT4 & TISSUE OPTICS PLUG-IN



A GAMOS plug-in for GEANT4 based Monte Carlo simulation of radiation-induced light transport in biological media

Adam K. Glaser, Stephen C. Kanick, Rongxiao Zhang, Pedro Arce, and Brian W. Pogue

Biomedical Optics EXPRESS

Glaser et al,
Biomed. Opt. Express (2013)

Optical dosimetry of radiotherapy beams using Cherenkov radiation: the relationship between light emission and dose

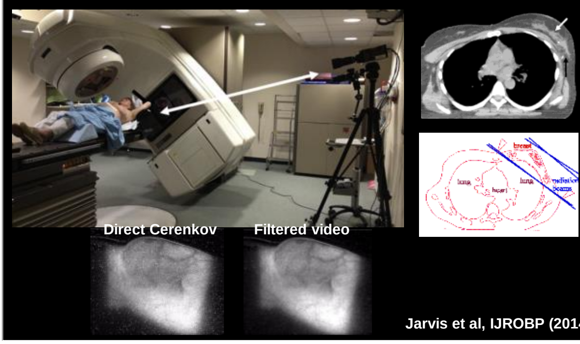
Adam K Glaser, Rongxiao Zhang, David J Gladstone and Brian W Pogue

Glaser et al,
Phys Med Biol 2014

Čerenkov in Humans

Čerenkov dose imaging

tracking skin dose with room lights on!

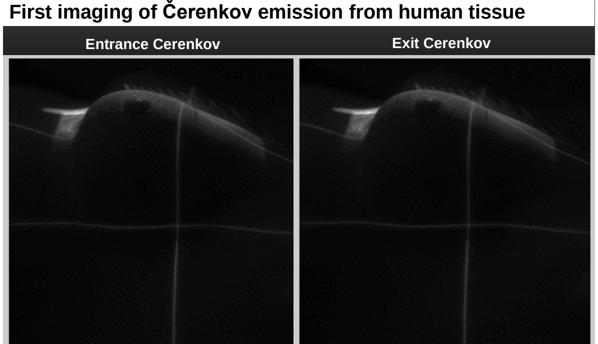


Jarvis et al, IJROBP (2014)

IMPROVEMENTS IN SNR TO ALLOW ČERENKOV IMAGING

Glaser et al, Optics Lett. 2012

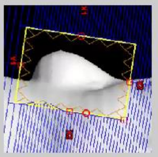
First imaging of Čerenkov emission from human tissue

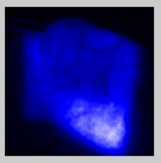


- **Whole breast radiotherapy with dynamic field.**
- **Real time monitoring possible.**

Jarvis et al, IJROBP (2014)

Dynamic beam field monitoring





Čerenkov emission identifies beam field dynamics due to MLC motion in real time (fps ~= 2.5).

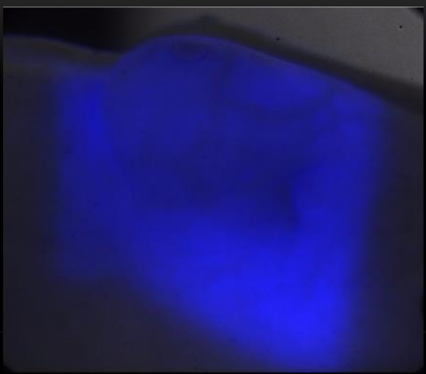
Jarvis et al, IJROBP (2014)

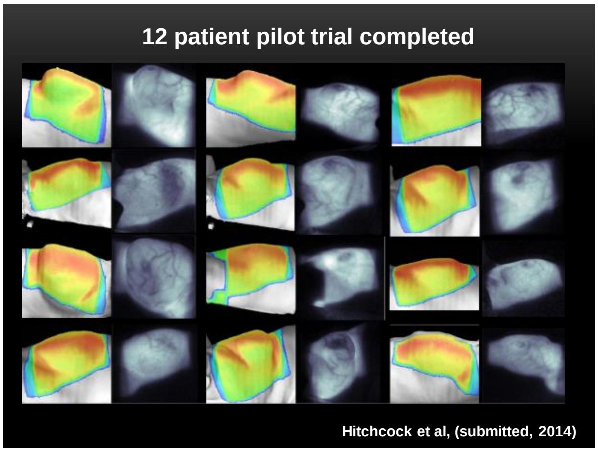
Options for Gated Cameras

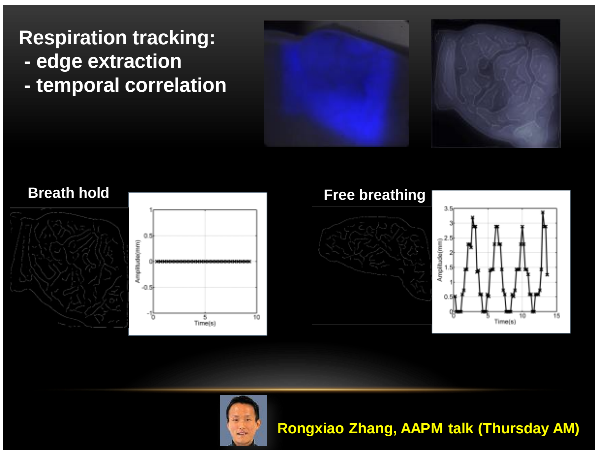
Camera Model	Sensor Type	Cost	Pixel Size (µm)	Resolution (pixels)	Gain	Gate Time	QE of Detector @ 700nm	QE of Intensifier @ 700 nm	Max Frame Rate
Basler acA1300-60gc	CMOS	$550	5.3 x 5.3	1280 x 1024	1	30 µs	42%	N/A	60
Canon EOS Rebel T3i	CMOS	$600	4.3 x 4.3	5184 x 3456	1	N/A	Not Listed	N/A	3.7
Apogee Alta F8300	CCD	$3k	5.4 x 5.4	3326 x 2504	1	N/A	42%	N/A	0.1
PIMAX3 1024i	ICCD	$55k	12.8 x 12.8	1024 x 1024	5	2 ns	27%	4%	27
PIMAX4 1024i	ICCD	$60k	12.8 x 12.9	1024 x 1024	21.54	2 ns	27%	25%	27
PIMAX4 512EM	EM-ICCD	$85k	16.0 x 16.0	512 x 512	10,000	2 ns	46%	25%	30

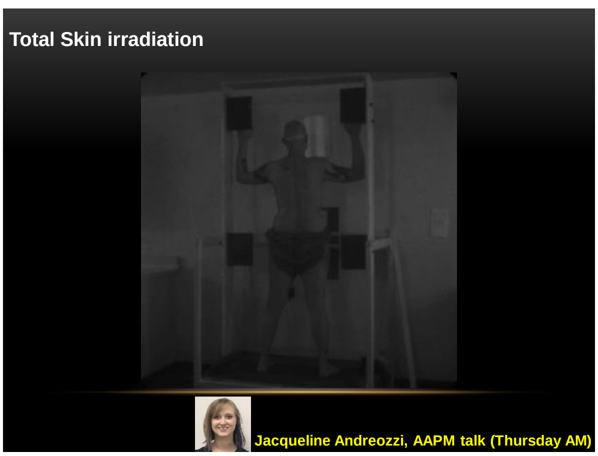
Jacqueline Andreozzi, AAPM talk (Thursday AM)

Video rate imaging (30 frames per second) with EM-ICCD



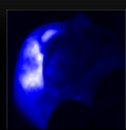

12 patient pilot trial completed
Hitchcock et al, (submitted, 2014)


Respiration tracking:
- edge extraction
- temporal correlation
Breath hold
Free breathing
Rongxiao Zhang, AAPM talk (Thursday AM)

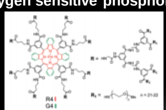

Total Skin irradiation
Jacqueline Andreozzi, AAPM talk (Thursday AM)

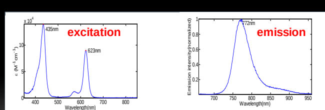
Molecular Imaging In Vivo ?

Use blue Čerenkov to excite NIR emitting molecular reporters in tissue



Oxygen sensitive phosphor

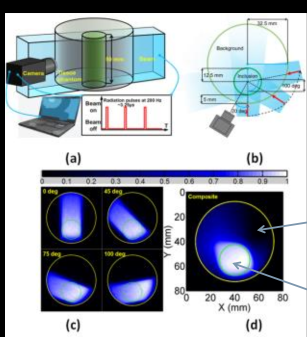




Sergei Vinogradov, UPenn

Zhang et al, J. Biomed Optics. 2013

Oxygen imaging with luminescence lifetime tomography



Lifetime recovery

τ = 44us
pO2 = 140mmHg

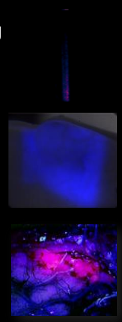
τ = 22us
pO2 = 5mmHg

Could be done with dose ≈ CT scan

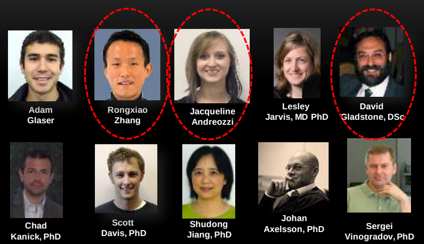
Holt et al, Phys Med Biol (in press)

SUMMARY:

1. Real-time water tank imaging
2. Real-time in vivo imaging
3. Molecular Sensing with γ-Čerenkov-luminscence



Čerenkography & Čerenkoscopy Team



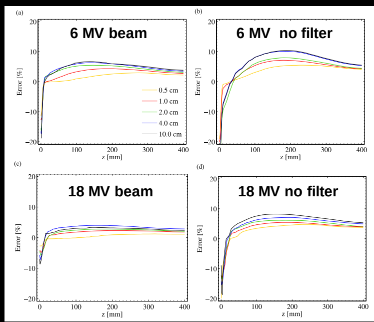
www.dartmouth.edu/optmed/

National Cancer Institute
R01 CA109558
R21 EB017559
Audrey Prouty Development Fund
Dartmouth-Hitchcock Norris Cotton Cancer Center
A National Cancer Institute Comprehensive Cancer Center

QUESTIONS?

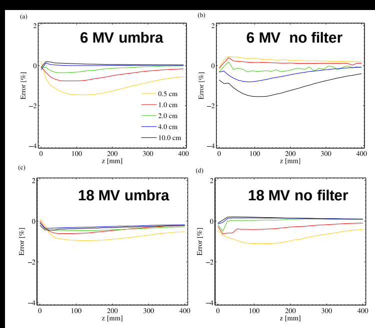
Geisel School of Medicine
Thayer School of Engineering at Dartmouth
Dartmouth-Hitchcock Norris Cotton Cancer Center
Wellman Center for Photomedicine

GEANT4 Monte Carlo: Dose vs. Cherenkov



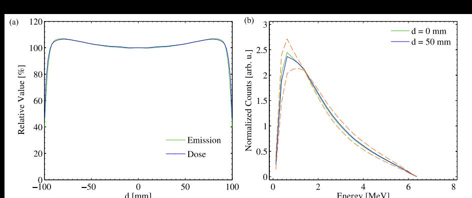
The relative error along the central axis between the Cherenkov light emission and dose for 0.5, 1.0, 2.0, 4.0, and 10.0 cm diameter beams for the 6X, 6FFF, 18X, and 18FFF beams

GEANT4 Monte Carlo: Dose vs. Cherenkov (umbra)

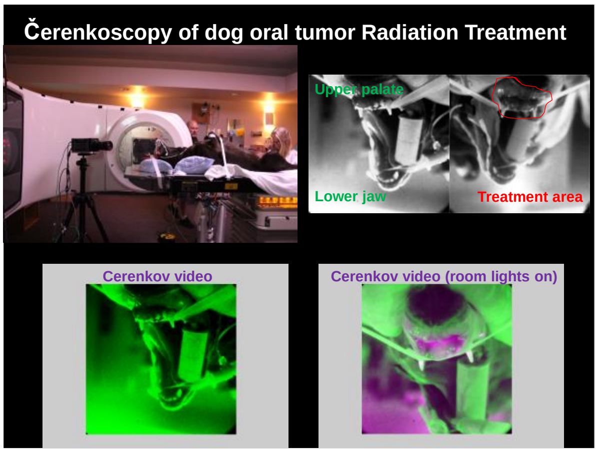


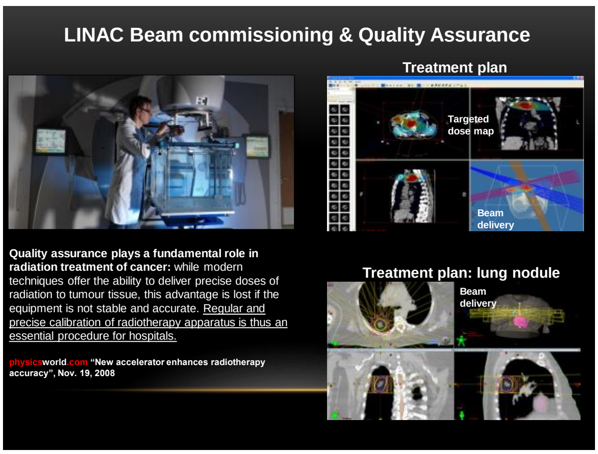
The relative error along the central axis between the Cherenkov light emission and dose for 0.5, 1.0, 2.0, 4.0, and 10.0 cm diameter beams for the 6X, 6FFF, 18X, and 18FFF beams

GEANT4 Monte Carlo: Dose vs. Cherenkov two parallel beams



(a) The central axis curve for the AP-PA treatment is plotted.
(b) The corresponding lateral curves at d_{max}, 50 cm, and at the isocenter (100 mm) are shown.


Čerenkoscopy of dog oral tumor Radiation Treatment
Upper palate
Lower jaw
Treatment area
Cerenkov video
Cerenkov video (room lights on)


LINAC Beam commissioning & Quality Assurance
Treatment plan
Targeted dose map
Beam delivery
Quality assurance plays a fundamental role in radiation treatment of cancer: while modern techniques offer the ability to deliver precise doses of radiation to tumour tissue, this advantage is lost if the equipment is not stable and accurate. Regular and precise calibration of radiotherapy apparatus is thus an essential procedure for hospitals.
physicsworld.com "New accelerator enhances radiotherapy accuracy", Nov. 19, 2008
Treatment plan: lung nodule
Beam delivery