Cerenkov Luminescence Endoscopy: Feasibility and Challenges

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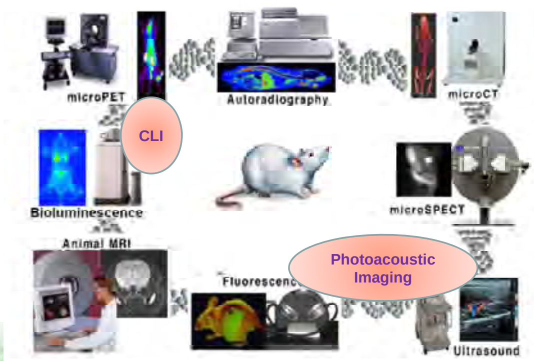
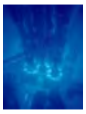
Multimodality Molecular Imaging



Massoud & Gambhir, Genes & Development, 2003

Cerenkov Radiation

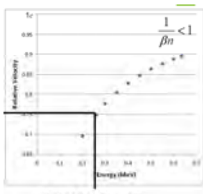


Cerenkov radiation is electromagnetic radiation emitted when a charged particle (such as an electron) passes through medium at a constant speed greater than the speed of light in this medium.

- During decay, a positron exits the nucleus at a speed that is governed by relativistic physics. The relativistic equation for kinetic energy, where m_0 is the rest mass energy

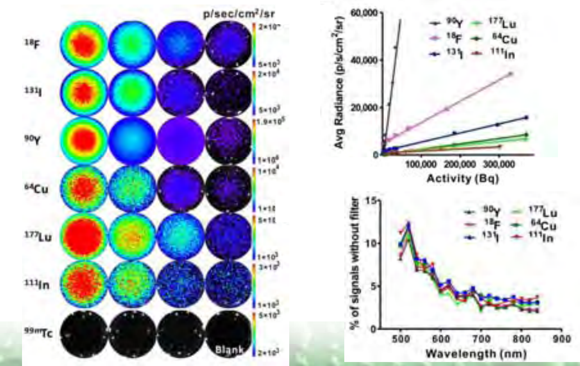
$$E = mc^2 - m_0c^2 \qquad E = mc^2\left[\frac{1}{\sqrt{1-v^2/c^2}} - 1\right]$$

- The relativistic velocity of a 0.635 MeV positron is 0.895c
- In water, the speed of light is 0.75c, positron exceeding this velocity will produce Cerenkov radiation



Robertson R., et al. PMB

CLI of Radionuclides



Liu H, et al. PLOS One, 2010

CLI for Plant Imaging

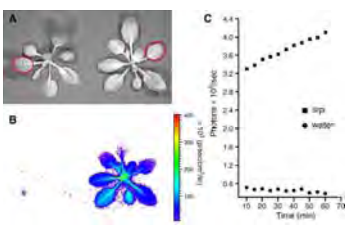
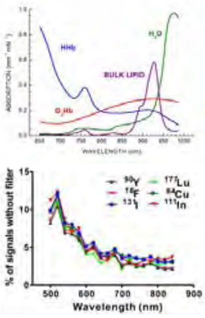


Fig. 3. (A) Photographic and (B) luminescence images of the plant (arabidopsis) at 10 min after immersion in control water (left) and [32P]phosphoric acid solution. (C) Time–activity curve of the activity in selected leaves (red oval in A).

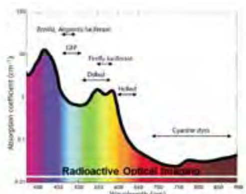
J.C. Park et al. / NMB

CLI for Small Animal Imaging



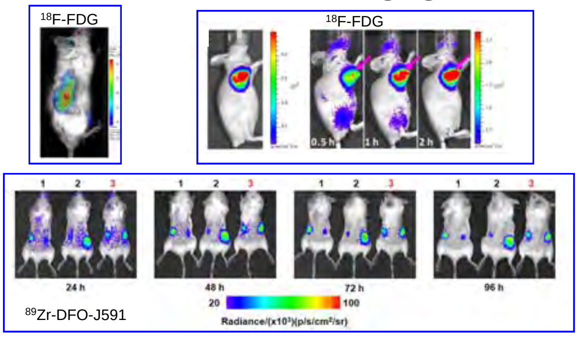
NIR Tissue Absorption

- **HHb** (deoxy-hemoglobin) = Hb not bound to O_2
- **O_2Hb** (oxy-hemoglobin) = Hb bound to O_2
- **H_2O** (water), unbound to proteins
- **Bulk Lipid**, in this example, oils



By fully usage of its continuous spectrum, CLI may provide better imaging than other fluorescence and luminescence imaging agents for both sensitivity and resolution. This might need development of better imaging instruments as well.

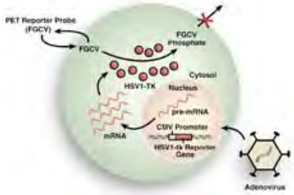
CLI for Tumor Imaging



Robertson, R., et al., Phys Med Biol, 2009
Liu H, et al. Plos One, 2010
Ruggiero, A., et al., J Nucl Med, 2010.

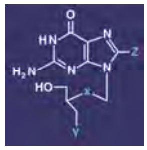
HSV1-tk/FGCV Reporter Gene/Reporter Probe System

HSV1-tk suicide gene, phosphorylates acycloguanosines, converting cycloguanosine monophosphate into diphosphates and triphosphates if present in sufficient concentration, kill cells by incorporation as chain-terminating derivatives or by direct inhibition of DNA polymerase



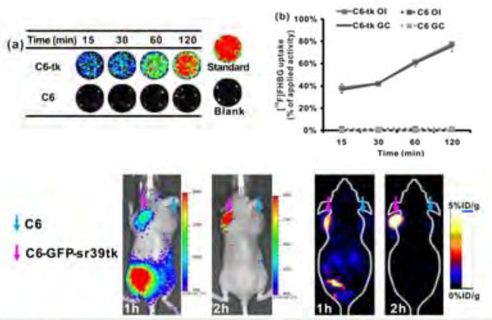
Substrates for HSV1-TK

Uracil nucleoside derivatives
Acycloguanosine analogs



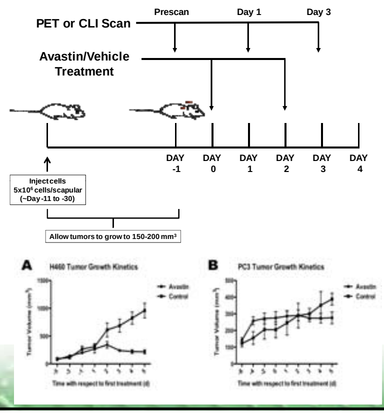
X=O, Y=OH, Z=H <GCV>
X=CH , Y=OH, Z=H <PCV>
<FGCV>
X=O, Y=OH, Z=F <FPCV>
X=CH , Y=OH, Z=F <FHPG>
X=O, Y=F, Z=H <FHBG>

CLI for Reporter Gene/Reporter Probe



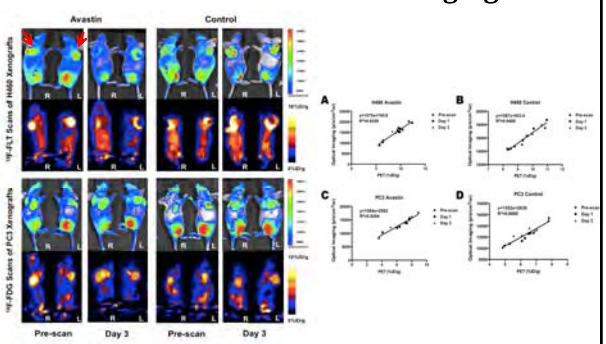
Liu H, et al. *Journal of Biomedical Optics*, 2010.

Tumor Treatment and Imaging



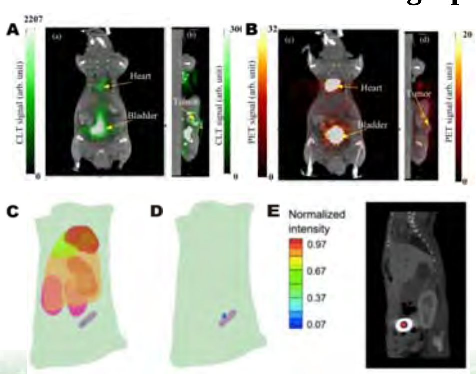
Xu Y, JNM, 2012 Feb;53(2):312-7

Tumor Treatment and Imaging

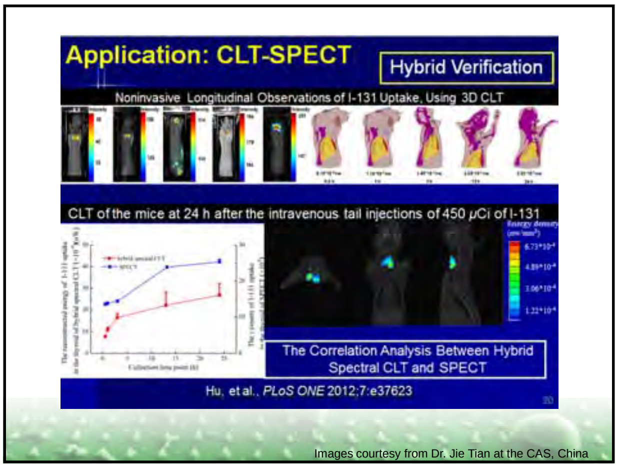


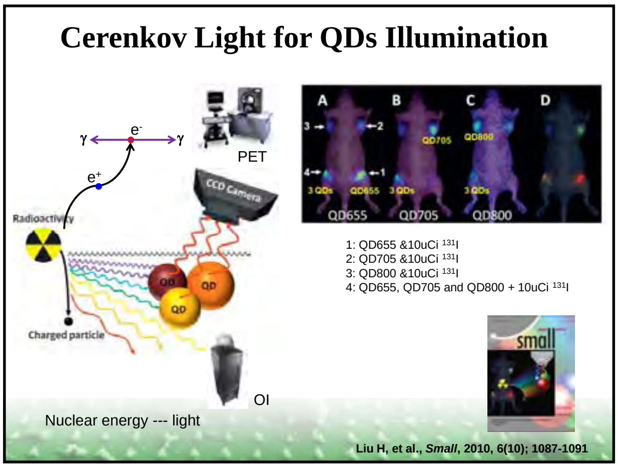
Xu Y, JNM, 2012 Feb;53(2):312-7

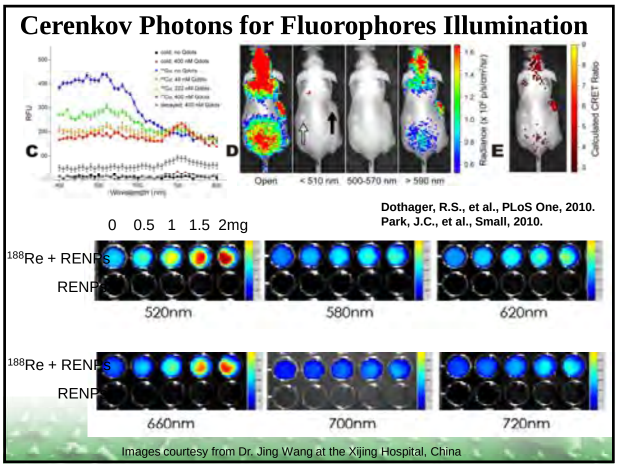
Cerenkov Luminescence Tomography

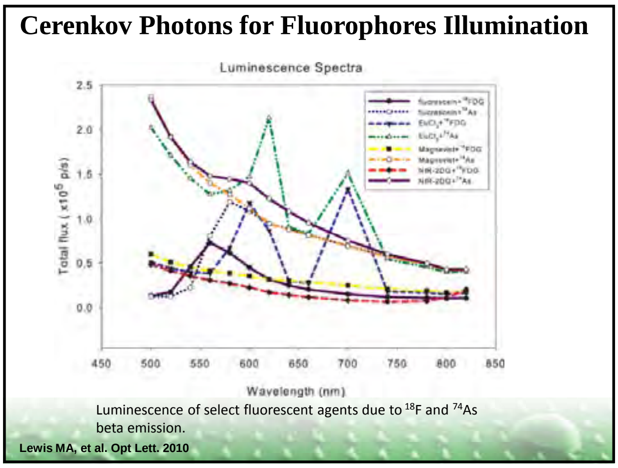


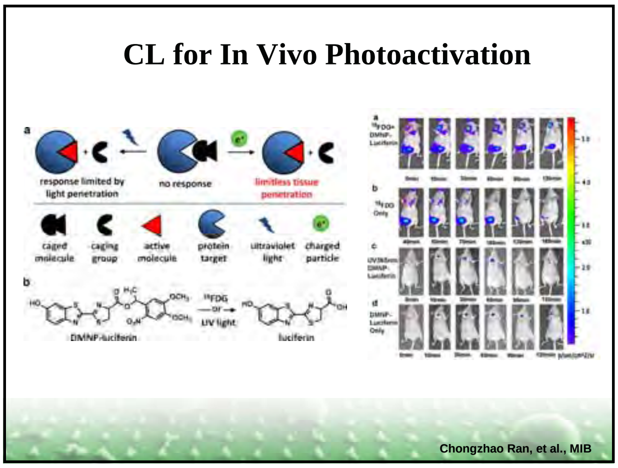
Li, C., et al. Opt Lett, 2010. Hu, Z., et al., Opt Express, 2010.

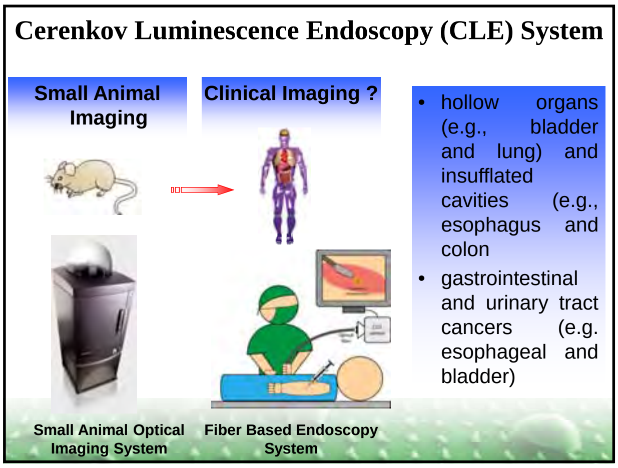

Application: CLT-SPECT
Hybrid Verification
Noninvasive Longitudinal Observations of I-131 Uptake, Using 3D CLT
CLT of the mice at 24 h after the intravenous tail injections of 450 μCi of I-131
The Correlation Analysis Between Hybrid Spectral CLT and SPECT
Hu, et al., PLoS ONE 2012;7:e37623
Images courtesy from Dr. Jie Tian at the CAS, China


Cerenkov Light for QDs Illumination
PET
CCD Camera
Radioactivity
Charged particle
QD
OI
Nuclear energy --- light
QD655
QD705
QD800
1: QD655 &10uCi 131I
2: QD705 &10uCi 131I
3: QD800 &10uCi 131I
4: QD655, QD705 and QD800 + 10uCi 131I
small
Liu H, et al., Small, 2010, 6(10); 1087-1091

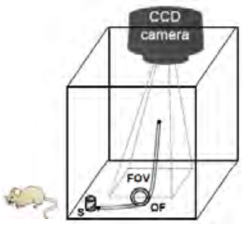

Cerenkov Photons for Fluorophores Illumination
Dothager, R.S., et al., PLoS One, 2010.
Park, J.C., et al., Small, 2010.
0 0.5 1 1.5 2mg
188Re + RENPs
RENPs
520nm
580nm
620nm
660nm
700nm
720nm
Images courtesy from Dr. Jing Wang at the Xijing Hospital, China


Cerenkov Photons for Fluorophores Illumination
Luminescence Spectra
Total flux (x10^5 p/s)
Wavelength (nm)
Luminescence of select fluorescent agents due to 18F and 74As beta emission.
Lewis MA, et al. Opt Lett. 2010


CL for In Vivo Photoactivation
response limited by light penetration
no response
limitless tissue penetration
caged molecule
caging group
active molecule
protein target
ultraviolet light
charged particle
DMNP-luciferin
luciferin
Chongzhao Ran, et al., MIB


Cerenkov Luminescence Endoscopy (CLE) System
Small Animal Imaging
Clinical Imaging ?
• hollow organs (e.g., bladder and lung) and insufflated cavities (e.g., esophagus and colon
• gastrointestinal and urinary tract cancers (e.g. esophageal and bladder)
Small Animal Optical Imaging System
Fiber Based Endoscopy System

Prototype CLE System



System:
an endoscope (optical fibers and/or optical lenses), a white light source, and a CCD

Fig. 1. IVIS-200 spectrum imaging system was adapted to image phantom samples/animal subjects (denoted by “S”), pre-administered with 18F-FDG, using different optical fibers/endoscopes (OF). The subject “S” is placed outside the rectangular field of view (FOV) of the imaging system. The input end of the OF is placed close to the subject “S”. The output end of the “OF” is facing the CCD camera such that CCD camera is focused on the output end.

Kothapalli S-R et al. Biomed. Opt. Exp., 2012; 3(6):1215-1225.
Poster Session 2, Abstract # P378; Control number: 1395713

Optical Endoscopes/Fibers

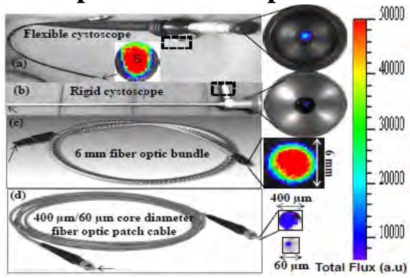
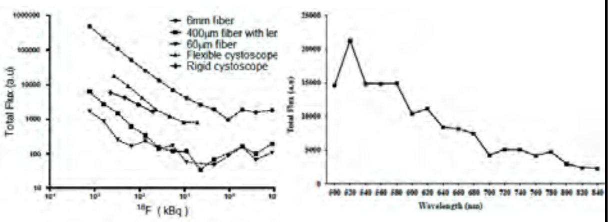


Table 1. Specifications of optical endoscopes/fibers used in the study

Instrument	Working Length	Numerical Aperture	Core Diameter	Fiber Material
Flexible Cystoscope	40 cm	in the range of 0.1 to 0.22	2 mm for image guide	not known
Rigid Cystoscope	30 cm	not known	2 mm for image guide	system of optical lenses and prisms; no fiber
6 mm fiber bundle	100 cm	0.22	6 mm	silica
400 µm fiber cable	100 cm	0.22	400 µm	silica
60 µm fiber cable	100 cm	0.22	60 µm	silica

Kothapalli S-R et al. Abstract # P378;

Detection Sensitivity of the CLE System

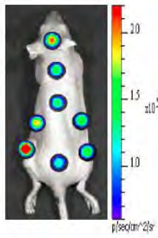


^{18}F-FDG: primary bladder tumor, SUV is ~4.5 (Ref). Thus 1 uCi of the probe is expected in 0.1 cc bladder cancer at 2 h p.i. of 10 mCi ^{18}F-FDG. Ref: EJNM, 2997:24(6):615-620.

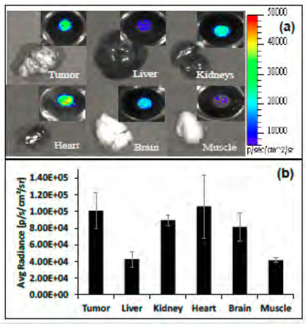
Improve detection sensitivity: specialty fibers that have high etendue (including high numerical aperture, larger diameter optic bundle, high packing fraction, low reflection and transmission losses); different radionuclides such as ^{90}Y; CCD/CMOS sensors

Kothapalli S-R et al. Abstract # P378;

In Vivo and Ex Vivo Imaging of Tumor Mice Using CLE System

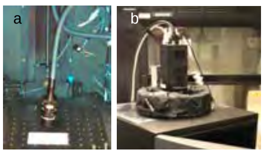


C6 Tumor
^{18}F-FDG
(940-970 uCi), 1h



Kothapalli S-R et al. Abstract # P378;

Custom Made Fiber Optic System for CLE

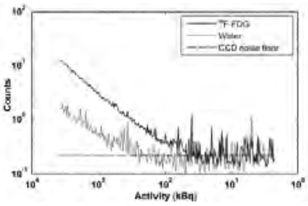


laparoscopic trocars

Fiber bundle
108 mm long
5 x 6.7 mm active area
discrete 10 um fibers

Intensified CCD
640 x 480 pixels
Single-photon imaging capability

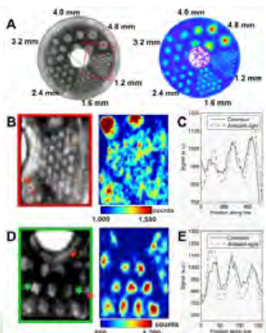
Sensitivity



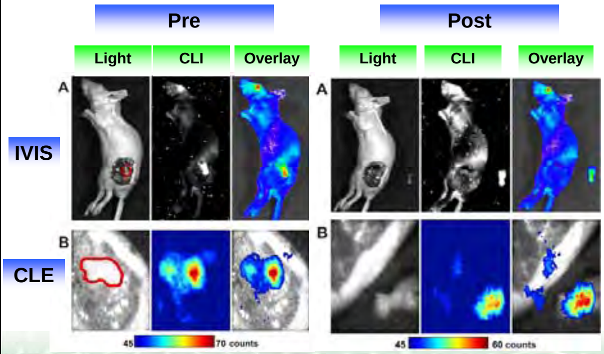
Fiber Based Prototype System

Liu H, et al. *JNM*. 2012 Aug 17. [Epub ahead of print] PMID: 22904353

Resolution of the CLE System



Imaging Using CLE System



295 µCi in mouse at imaging time

2.3 µCi in tumor at imaging time

Feasibility and Challenges of CLE

- Probes available
- Clinical translatable
- Easy to use
- Economically viable
- High Resolution
- Inherited multimodality imaging method

- Radioactive
- Optical imaging modality (low tissue penetration, scattering..)
- Relatively low sensitivity

Summary

- We demonstrate that Cerenkov light can be coupled and transmitted through different clinical endoscopes and conventional optical fibers for potential applications during clinical endoscopy
- Cerenkov light from as low as 1 µCi of radioactivity emitted from ^{18}F-FDG was reliably detected using a 6 mm fiber optic bundle.
- Our results support additional investigations of CLI as a promising modality for endoscopic molecular imaging.

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MIPS Molecular Imaging Program at Stanford

Stanford University School of Medicine Department of Radiology