Wake Forest Baptist Medical Center

Molecular Imaging and Theranostics

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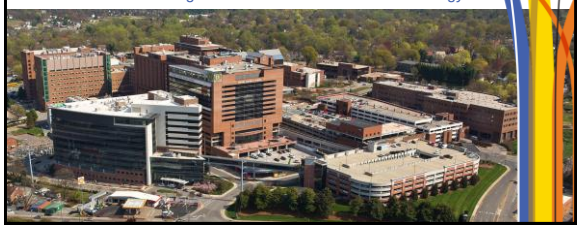
Senior Associate Dean of Clinical and Translational Research
Isadore Meschan Distinguished Professor & Chair of Radiology



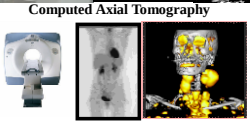
Modern Medical Imaging

Magnetic Resonance Imaging

Digital Radiography and Angiography

Computed Axial Tomography

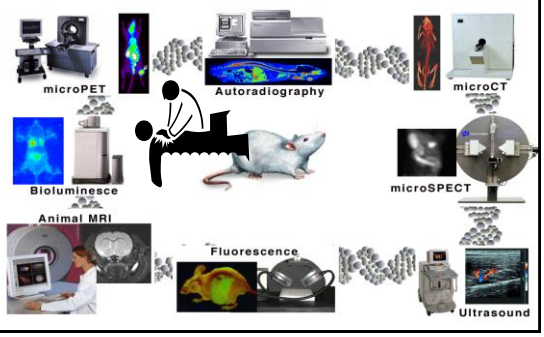
Ultrasonography



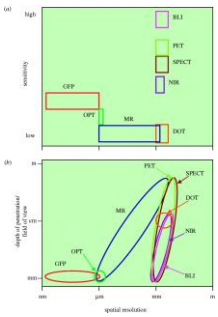
Positron Emission Tomography

Interventional Radiology

Small Animal Imaging Systems



(a) Comparison of sensitivity versus spatial resolution and (b) depth of penetration/field of view versus spatial resolution for the different molecular imaging modalities.



Cassidy P J, Radda G K J. R. Soc. Interface 2005;2:133-144

Interface

Table 1 | **Overview of high-resolution, small-animal imaging systems**

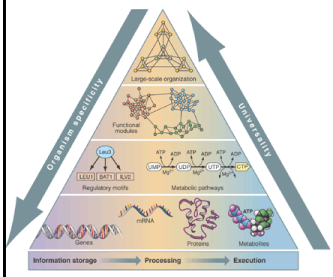
Technique	Resolution	Depth	Time	Imaging agents	Target*	Cost‡	Primary small-animal use	Clinical use
MR	10–100 μm	No limit	Minutes–hours	Gadolinium, dysprosium, iron oxide particles	A, P, M	$$$	Versatile imaging modality with high soft-tissue contrast	Yes
CT	50 μm	No limit	Minutes	Iodine	A, P	$$	Lung and bone imaging	Yes
Ultrasound	50 μm	Millimetres	Minutes	Microbubbles	A, P	$$	Vascular and interventional imaging	Yes
PET	1–2 mm	No limit	Minutes	^{18}F, ^{11}C, ^{15}O	P, M	$$$	Versatile imaging modality with many different tracers	Yes
SPECT	1–2 mm	No limit	Minutes	^{99m}Tc, ^{111}In chelates	P, M	$$	Commonly used to image labelled antibodies, peptides and so on	Yes
FRI	2–3 mm	<1 cm	Seconds–minutes	Photoproteins (GFP), NIR fluorochromes	P, M	$	Rapid screening of molecular events in surface-based tumours	Development
FMT	1 mm	<10 cm	Seconds–minutes	NIR fluorochromes	P, M	$$	Quantitative imaging of targeted or 'smart' fluorochrome reporters in deep tumours	Development
BLI	Several millimetres	Centimetres	Minutes	Luciferins	M	$$	Gene expression, cell and bacterial tracking	No
Intravital microscopy (confocal, multiphoton)	1 μm	<400 μm	Seconds–minutes	Photoproteins (GFP), Fluorochromes	P, M	$$$	All of the above at higher resolutions but at limited depths and coverage	Limited development (skin)

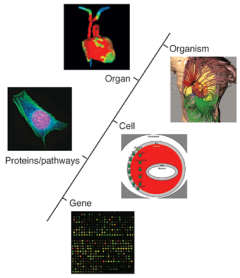
*Primary area that a given imaging modality interrogates: A, anatomical; M, molecular; P, physiological. ‡Cost of system: $ <100,000; $$ 100–300,000; $$$ >300,000. BLI, bioluminescence imaging; CT, X-ray computed tomography; FMT, fluorescence-mediated molecular tomography; FRI, fluorescence reflectance imaging; GFP, green fluorescent protein; NIR, near-infrared; MR, magnetic resonance; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Rudin M, et al. Nature Reviews/Drug Discovery 2003; 2:123-131

Imaging Probes: Concentration Requirements for Different Imaging Modalities

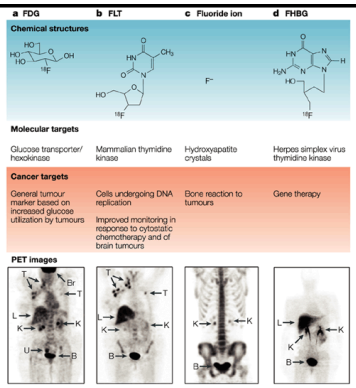
Imaging Technique	Sensitivity
PET	10^{-11}-10^{-12} mole/L
SPECT	10^{-10}-10^{-11} mole/L
Bioluminescence	10^{-15}-10^{-17} mole/L
Fluorescence	10^{-9}-10^{-12} mole/L
MRI	10^{-3}-10^{-5} mole/L
CT	Not well characterized
Ultrasound	Not well characterized



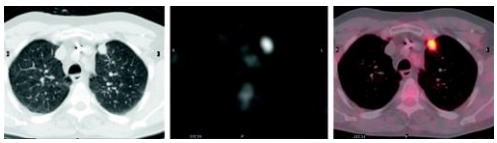


Oltvai ZN, Barabasi A. Science 2002; 298:763-764.

Pennisi E. Science 2003;302:1648-9.

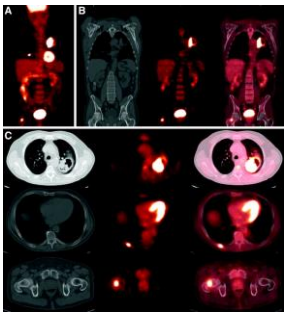


Gambhir SS. Nat Reviews Cancer 2003;2:683-693.



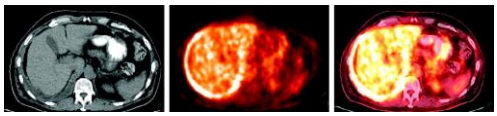
Solitary pulmonary nodule with spiculated borders in left upper lobe. Tira Bunyaviroch, and R. Edward Coleman J Nucl Med 2006;47:451-469

JNM The Journal of NUCLEAR MEDICINE



Lung cancer with osseous metastases. Tira Bunyaviroch, and R. Edward Coleman J Nucl Med 2006;47:451-469

JNM The Journal of NUCLEAR MEDICINE



Malignant pleural effusion in right hemithorax. Tira Bunyaviroch, and R. Edward Coleman J Nucl Med 2006;47:451-469

JNM The Journal of NUCLEAR MEDICINE

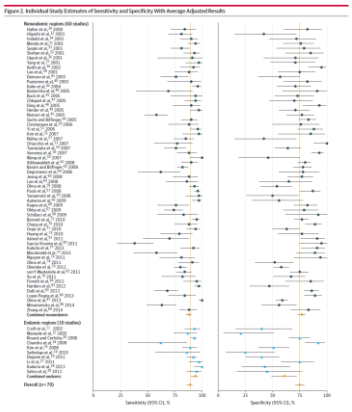
Original Investigation

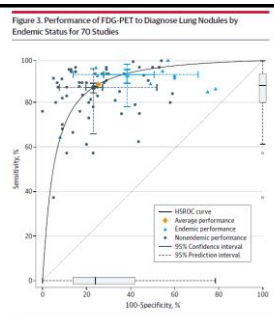
Accuracy of FDG-PET to Diagnose Lung Cancer in Areas With Infectious Lung Disease
A Meta-analysis

Stephen A. Deppen, PhD; Jeffrey D. Blume, PhD; Clark D. Kensinger, MD; Ashley M. Morgan, BE; Melinda C. Aldrich, PhD, MPH; Pierre P. Massion, MD; Ronald C. Walker, MD; Melissa L. McPheeters, PhD, MPH; Joe B. Putnam Jr, MD; Eric L. Grogan, MD, MPH

RESULTS Heterogeneity for sensitivity (I^2 = 87%) and specificity (I^2 = 82%) was observed across studies. The pooled (unadjusted) sensitivity was 89% (95% CI, 86%-91%) and specificity was 75% (95% CI, 71%-79%). There was a 16 percentage point-lower average adjusted specificity in regions with endemic infectious lung disease (61% [95% CI, 49%-72%]) compared with nonendemic regions (77% [95% CI, 73%-80%]). Lower specificity was observed when the analysis was limited to rigorously conducted and well-controlled studies. In general, sensitivity did not change appreciably by endemic infection status, even after adjusting for relevant factors.

JAMA. 2014;312(12):1227-1236. doi:10.1001/jama.2014.11488





The operating points for endemic and nonendemic infectious lung disease studies and 95% confidence and prediction intervals for those operating points are shown. The horizontal box and whiskers plot represents the distribution of study specificity, and the vertical box and whiskers plot represents the distribution of study sensitivity. The box limits are the closest data point to the interquartile range of 25% and 75% with the bar being the median (50%). Error bar whiskers represent the data point closest to 1.5 times the interquartile range and the dots outside the whiskers represent outlier study values. FDG indicates fludeoxyglucose F 18; HSROC, hierarchical summary receiver operator curve; PET, positron emission tomography.

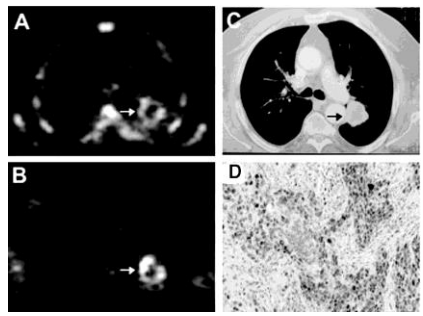
Eur J Nucl Med Mol Imaging (2015) 42:241–251
DOI 10.1007/s00259-014-2903-7

ORIGINAL ARTICLE

Prognostic value of volumetric parameters of ^{18}F-FDG PET in non-small-cell lung cancer: a meta-analysis

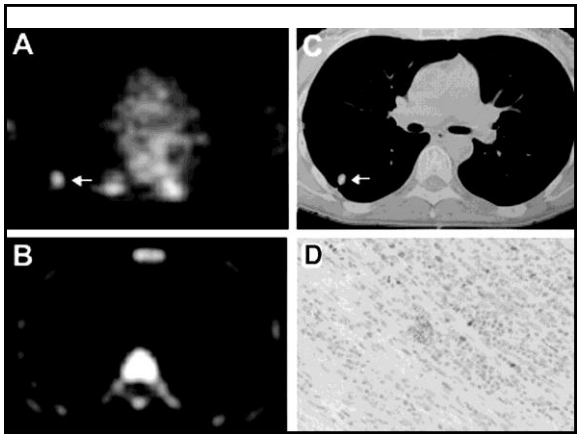
Hyung-Jun Im · Kyoungjune Pak · Gi Jeong Cheon · Keon Wook Kang · Seong-Jang Kim · In-Joo Kim · June-Key Chung · E. Edmund Kim · Dong Soo Lee

Results Thirteen eligible studies including 1,581 patients were analysed. Patients with high MTV showed a worse prognosis with an HR of 2.71 (95 % CI 1.82 – 4.02, $p<0.00001$) for adverse events and an HR of 2.31 (95 % CI 1.54 – 3.47, $p<0.00001$) for death. Patients with high TLG also showed a worse prognosis with an HR of 2.35 (95 % CI 1.91 – 2.89, $p<0.00001$) for adverse events and an HR of 2.43 (95 % CI 1.89 – 3.11, $p<0.00001$) for death. The prognostic value of MTV and TLG remained significant in a subgroup analysis according to TNM stage as well as the methods for defining cut-off values and tumour delineation.



Patient 5, with NSCLC in left upper lobe. Andreas K. Buck et al. J Nucl Med 2003;44:1426-1431

JNM The Journal of NUCLEAR MEDICINE



MOLECULAR AND CLINICAL ONCOLOGY 3: 101-108, 2015

Comparison of the diagnostic performance of ^{18}F-fluorothymidine versus ^{18}F-fluorodeoxyglucose positron emission tomography on pulmonary lesions: A meta analysis

XIAO-FENG LI, DONG DAI, XIU-YU SONG, JIAN-JING LIU, YAN-JIA ZHU and WEN-GUI XU

Department of Molecular Imaging and Nuclear Medicine, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin 300060, P.R. China

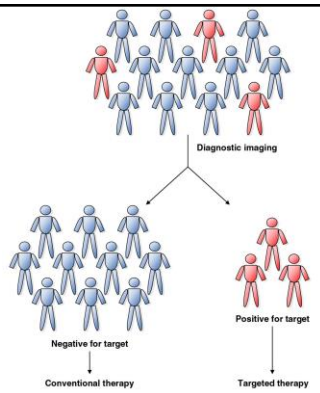
of linear model. The meta analysis showed that ^{18}F-FLT PET had a higher specificity (0.70; 95% CI, 0.61-0.77), but lower sensitivity (0.81; 95% CI, 0.74-0.87) compared to ^{18}F-FDG PET (0.50; 95% CI, 0.41-0.58 for specificity; 0.92; 95% CI 0.86-0.95 for sensitivity). For DOR, ^{18}F-FLT PET (12.58; 95% CI, 6.81-23.24) was higher compared to ^{18}F-FDG PET (10.72; 95% CI, 5.51-20.87). The area under the curve was 0.8592 and 0.9240 for ^{18}F-FLT PET and ^{18}F-FDG PET, respectively (Z=0.976, P>0.05). In conclusion, ^{18}F-FLT PET and ^{18}F-FDG PET had good diagnostic performance for the overall assessment of pulmonary lesions, and ^{18}F-FLT PET had a higher specificity compared to ^{18}F-FDG PET, but was less sensitive than ^{18}F-FDG PET. Therefore, ^{18}F-FLT and ^{18}F-FDG together could add diagnostic confidence for pulmonary lesions.

What is Molecular Theranostics?

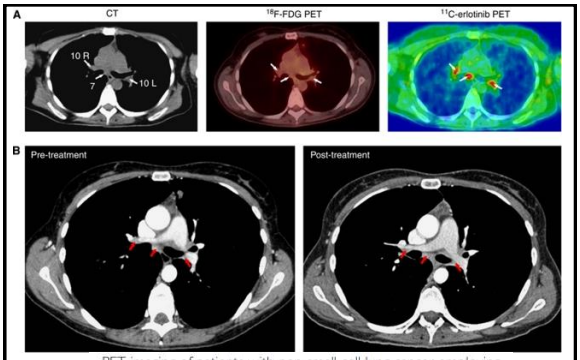
- Treatment strategy that combines diagnostics and therapeutics
- Originally used to describe process of diagnostic therapy for individual patients for drug testing
- Important component of personalized medicine
- Imagers can approach theranostics from the imaging perspective with combined therapy

Current "Molecular Theranostic"

- Iodine –radionuclide for thyroid imaging; and treatment of treatment of thyroid disease and cancer
- Radiolabeled octreotide for somatostatin receptor imaging and treatment of SSTR cancers
- CD20-specific monocloncal antibody labeled with radionuclide for imaging and therapy

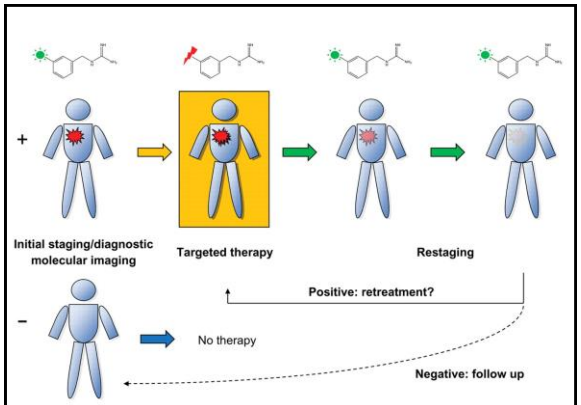


Lee DY, Li KCP. AJR 2011;197:318-324.

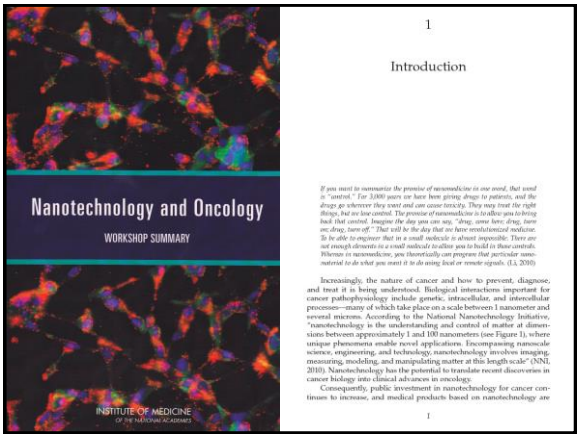


PET imaging of patients with non-small cell lung cancer employing an EGF receptor targeting drug as tracer **BJC 2011; 105:1850-55**

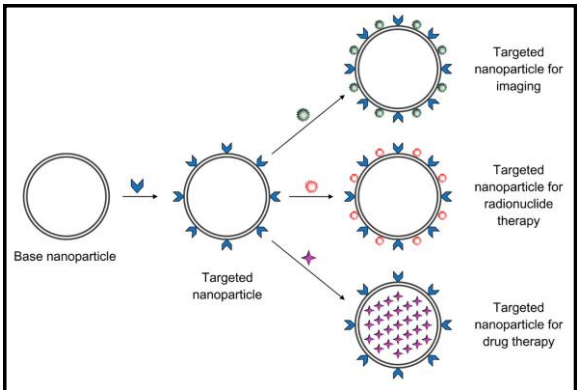
AA Memon[1], B Weber[1,2], M Winterdahl[1], S Jakobsen[3], P Meldgaard[3], HHT Madsen[4], S Keiding[3], E Nexo[5,1] and BS Sorensen[1]



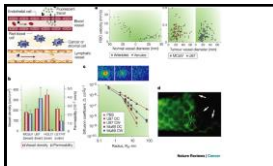
Lee DY, Li KCP. AJR 2011;197:318-324.



If you want to summarize the promise of nanomedicine in one word, that word is "control." For 3,000 years we have been giving drugs to patients, and the drugs go wherever they want and can cause toxicity. They may treat the right things, but we lose control. The promise of nanomedicine is to allow you to bring back that control. Imagine the day you can say, "drug, come here; drug, turn on; drug, turn off." That will be the day that we have revolutionized medicine. To be able to engineer that in a small molecule is almost impossible. There are not enough elements in a small molecule to allow you to build in those controls. Whereas in nanomedicine, you theoretically can program that particular nano-material to do what you want it to do using local or remote signals. (Li, 2010)

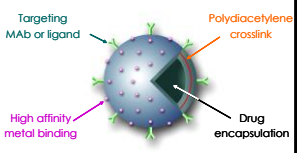


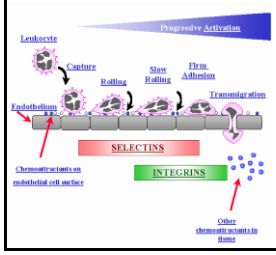
Lee DY, Li KCP. AJR 2011;197:318-324.

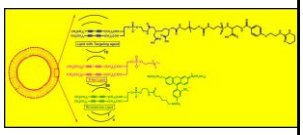


Jain RK, et al. Nature Reviews 2002;2:266-276

A Nanoscale Targeted PV

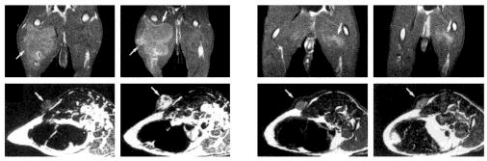






Molecular Imaging of Angiogenesis

LM609-PV pre post | Isotype Ab-PV pre post



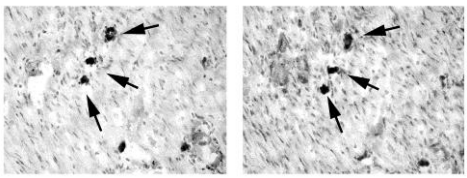
T1w MRI images: Vx2 carcinoma rabbit model

Sipkins DA, et al. Nature Medicine 1998;4:623-626.

Intravascular Confinement

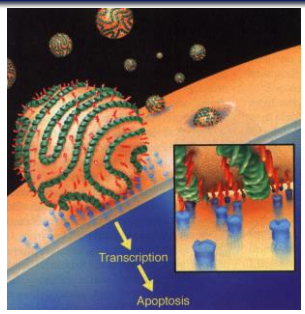
Immunohistochemistry of tumor periphery

Integrin $\alpha_v\beta_3$ | PV-anti-$\alpha_v\beta_3$ conjugate



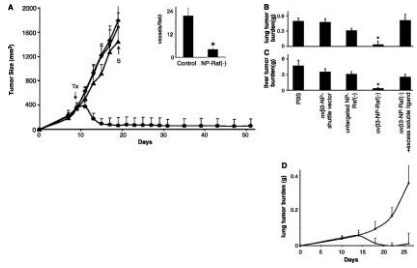
Sipkins DA, et al. Nature Medicine 1998;4:623-626.

Vascular Targeted Gene Therapy

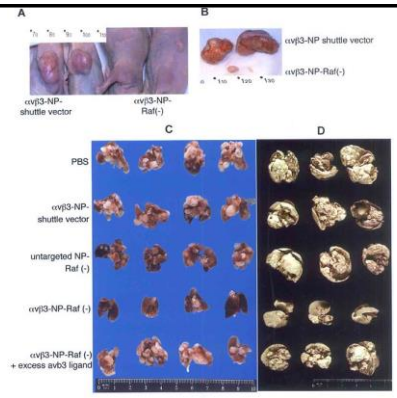


Couzin J. Science 2002;296:2314-2315.

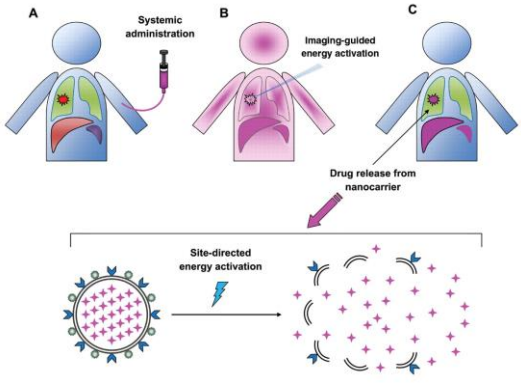
Vascular-targeted Gene Therapy



Hood JD, Bednarski M, et al. Science 2002; 296:2404-2407.

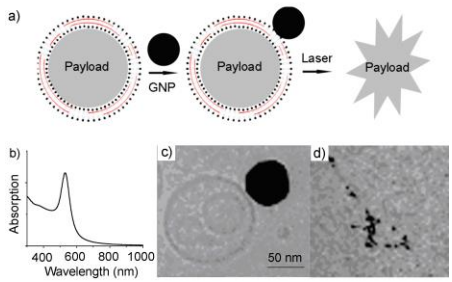


Hood JD, Bednarski M, et al. Science 2002; 296:2404-2407.



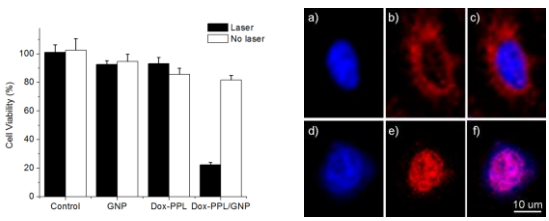
Lee DY, Li KCP. AJR 2011;197:318-324.

Drug Release Process



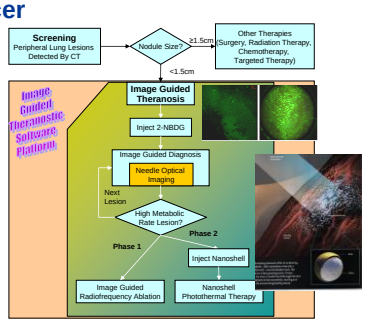
Qin G, et al. Nanotechnology 2011;22:155605. Epub 2011 Mar 10.

Laser triggered Au-Dox-PPLs Influence on Pharmacodynamics in MDA-MB-231 cells



Qin G, et al. Nanotechnology 2011;22:155605. Epub 2011 Mar 10.

Systems Approach of Image-guided Theranostic for Peripheral Lung Cancer



In collaborating with Bioengineering, Rice University and Philips Medical Systems