MOLECULAR IMAGING

Functional Imaging Methods
Multi-Modality

Máthé, Domokos PhD

Overview

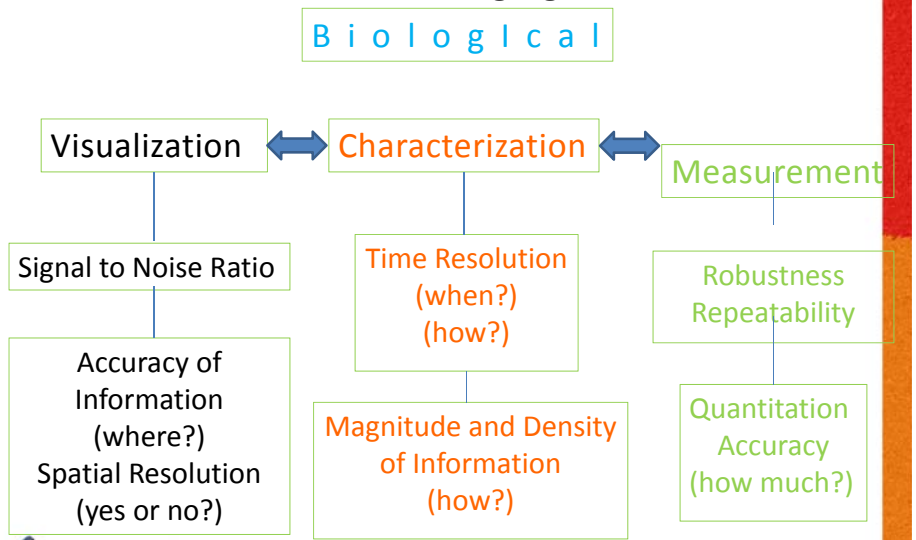
- What do we call molecular imaging and why?
- What can we exploit to obtain molecular imaging data?
- Research-oriented molecular imaging methodologies (in general)
- Clinical application possibilities of molecular imaging
  (screening, diagnostics, personalized therapy, monitoring/follow-up)
- Most actually important methods in M.I., outlook for tomorrow
  PET, SPECT, MRI, Planar Fluorescence, Optical Tomographies)
  Oncology, neuroscience, cardiovascular medicine, reumatology, endocrinology, surgery
- Correlation of functional and morphological information
- PACS and clinical relevance of image segmentation/registration

- Molecular Biology + In-Vivo Non-Invasive Imaging?

  “Imaging is the extraction of information in time and space at all levels of biological organization"
  (Dr. Elias Zerhouni, XIVth NIH Director)

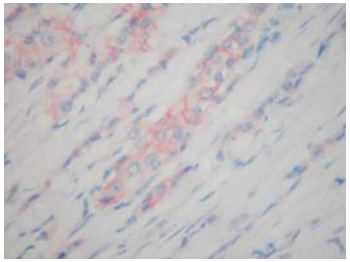
  “Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems.”
  (definition by the U.S. Society of Nuclear Medicine and Molecular Imaging)

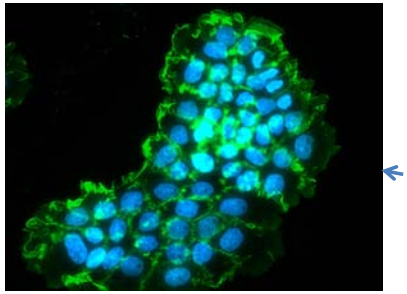
Molecular Imaging Ideals:



Microscopy: Immunohistochemistry, immunofluorescence

IHC: Targeted ntibody reacts with somatostatin 2a receptors over-expressed in insulinoma (300x, H&E counterstain, reaction is RED)

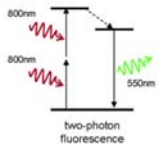


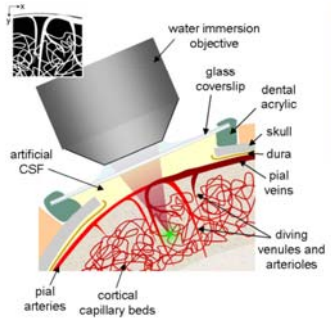


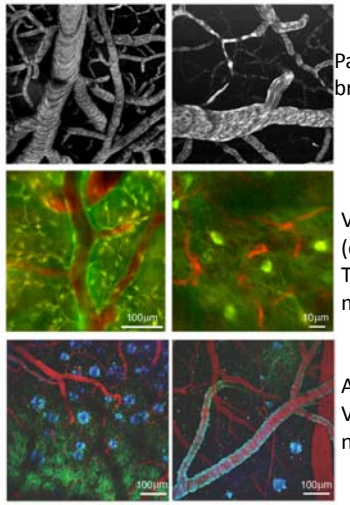
A431 epithelial cc. tumor cells, nuclei stained with Hoechst-blue, PHOSPHORILATED EGF receptors in cell membrane are GREEN using an antibody coupled to 488 nm emission DyLight fluorescent stain

High definition methods in live animals: in vivo dual photon microscopy

better S/N ratio
increased resolution





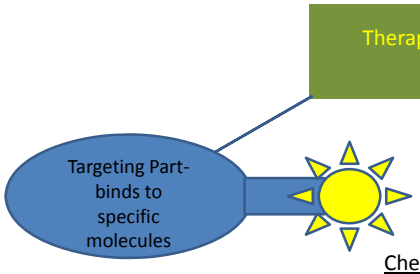


Pattern of RBC flow in brain vessels

Vessels and neurons (dextran Texas Red and GFP-TG mouse)

Amiloid plaques (Blue), Vessels (red) neurons(green)

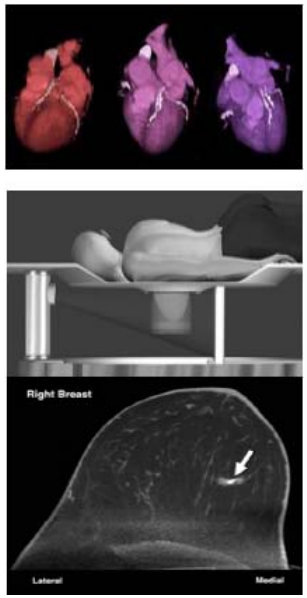
General Structure of a Molecular Probe



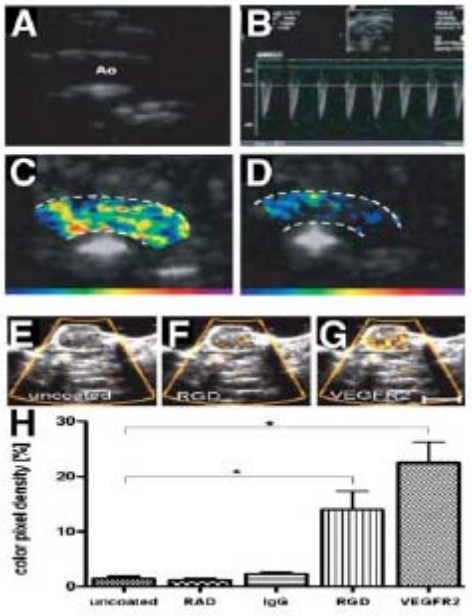
Small Molecules
Peptides
Proteins/Subunits
Antibodies/Subunits

<u>Chemical Nature:</u>
PET/SPECT: isotopes (radioactivity)
Optical/Acoustic: Fluorescent Dyes
MRI: Gd, Fe
CT: iodine, Barium sulphate
<u>Nano/microparticles:</u>
Optical: quantum dot, carbon nanotubes, Au particles
MRI: iron and Mn-oxide particles
CT: golden particles

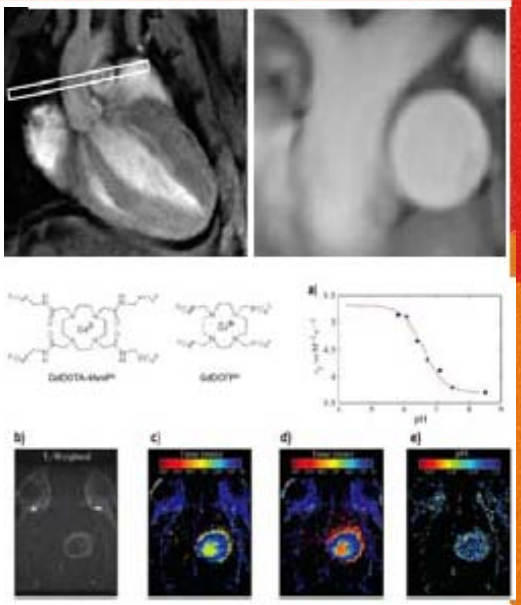
CT	3D Attenuation Map of X-Rays
Advantages	Any Imaging Depth Good Resolution Simple Medium-Priced Sub-minute scan times
Disadvantages	Radiation Dose Soft Tissue C. Just anatomical and functional images Any imaging depth Good Resolution WB Imaging Minute Scanning Time Semi-Expensive Anatomy
Contrast Materials	Ba, I, Kr, Xe, Au
Clinical Use	Tumor perfusion, Ca-score, Ventillation
Voxel Sizes, Cells Per Voxel	1x1x1 mm 1 million



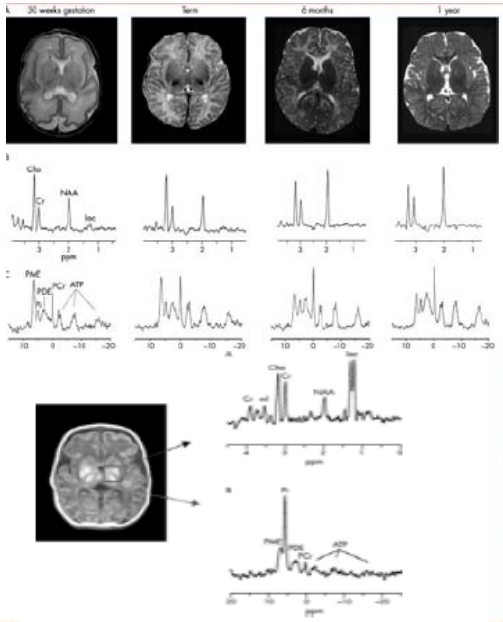
UltraSound	3D differences in echo and spreading of sound waves
Advantages	No ionizing radiation Fast/RT imaging High Sensitivity High Resolution Cheap
Disadvantages	No WB img. Only vascular contrast materials Operator dependency
Contrast Materials	Micro-Bubbles
Clinical Use	Focal liver lesions, Echocardiography, Blood perfusion…Rare, Prostate Cancer VEFG Expression (Phase III BR55)
Voxel Sizes, Cells Per Voxel	1x1x1 mm 1 million



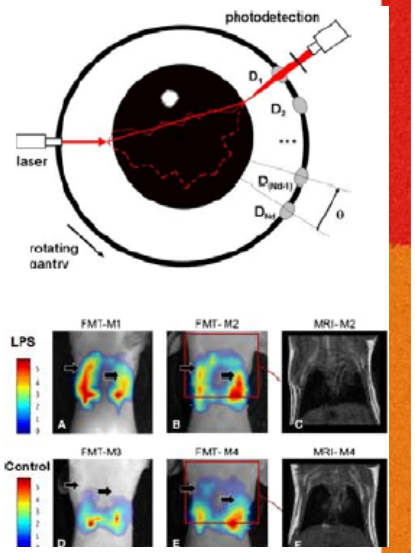
MRI (IRM…)	3D / 2D Image of Proton Spins
Advantages	Any Imaging Depth and Plane WB Imaging No ionizing radiation High Soft Tissue Contrast
Disadvantages	Expensive Low Sensitivity Long imaging time
Contrast Materials	Gd3+, iron-oxide particles (SPIO, USPIO)
Clinical Use	Liver, Brain Lesions, Cardio-MRI
Voxel Sizes, Cells Per Voxel	1x1x1 mm 10^{13}



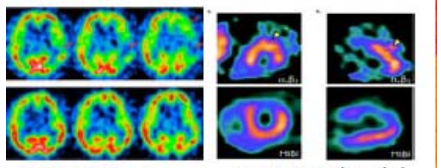
MRS	Recorded Electromagnetic Resonance Spectrum
Advantages	No ionizing radiation WB Imaging
Disadvantages	Expensive Very low sensitivity External Calibration / Special Knowledge
Contrast Materials	Cholin, Lactate, Creatin, Lipids, N-Ac-Aspartate
Clinical Use	Brain Tumor Stratification, Stroke
Voxel Sizes, Cells Per Voxel	N.A.



Optical Methods	Visible/NIR Light Transmission/Reflectance/Emission/ Scatter in 2D , 3D
Advantages	No ionizing radiation Short/RT Imaging High Spatial Resolution Very Sensitive, Semi-Quantitative Multiplex
Disadvantages	Limited Transparency No WB imaging
Contrast Materials	Fluorescent molecules, Light-emitting reactions, Dyes, QD-s, NP-s
Clinical Use	Experimental, Sentinel Ln., Image-Guided Surgery, Retinopathies (OCT), Mammary screnning (LumaGem)
Voxel Sizes, Cells Per Voxel	2D: 0.01 mm2 3D: 0.8x0.8x0.8 cm 10^3 (2D), 10^{13} (3D): cca.10^{4-5} per cell

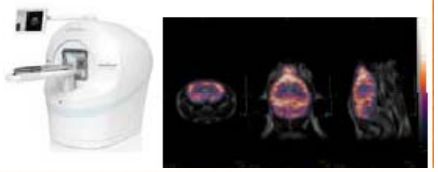


SPECT	3D Gamma-ray Source Array in Tissue
Advantages	Any imaging depth WB Imaging Quantitative Good resolution Multiplexing Theragnostics Combination w/CT
Disadvantages	Radiation Dose Sub-mm Resol. Long imaging times
Contrast Materials	Tc-99m, I-123, In-111, Lu-177, Ho-166, Tl-201
Clinical Use	Nuclear Cardiology, Brain Perfusion, Oncology (AB, Peptides), Receptor T.
Voxel Sizes, Cells Per Voxel	Clinical: 0.8 x 0.8 x0.8 mm Small A: 0.3 x 0.3 x 0.3 mm 2 pM / voxel 1/10 atom per cell

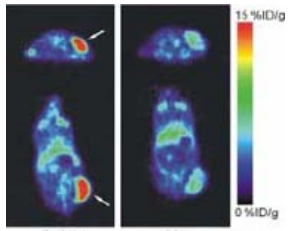


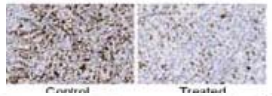
I-123 iomazenil agyi SPECT

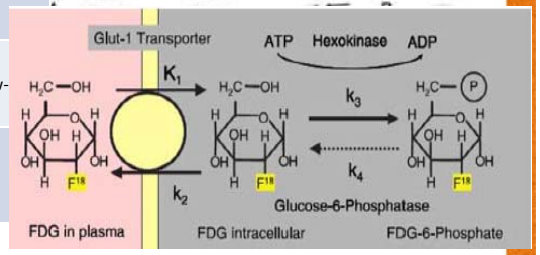
Tc-99m-MIBI szív perfúzió + angioneogenezis SPECT I-123-integrin liganddal



PET	3D 511 keV Gamma-ray Source Array in Tissue
Advantages	Any imaging depth WB Imaging Quantitative Anatomical Co-registration CT, MRI
Disadvantages	Radiation Dose PRICE Resolution Longer imaging times
Contrast Materials	C-11, F-18, Ga-68, Cu-64, Zr-89
Clinical Use	FDG Patient Staging+Follow-
Voxel Sizes, Cells Per Voxel	5 x 5x 5 mm 0.6 x 0.6 x 0.6 mm 0.02 pM/voxel 1/100 atom per cell



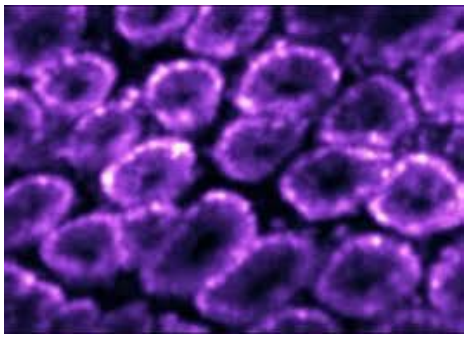




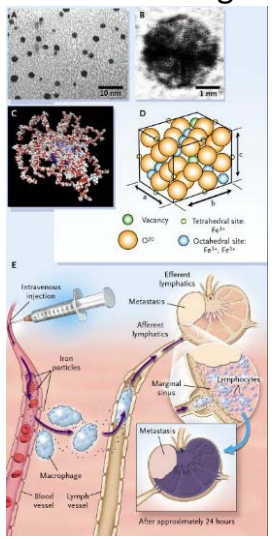
Screening-Confocal Endomicroscopy

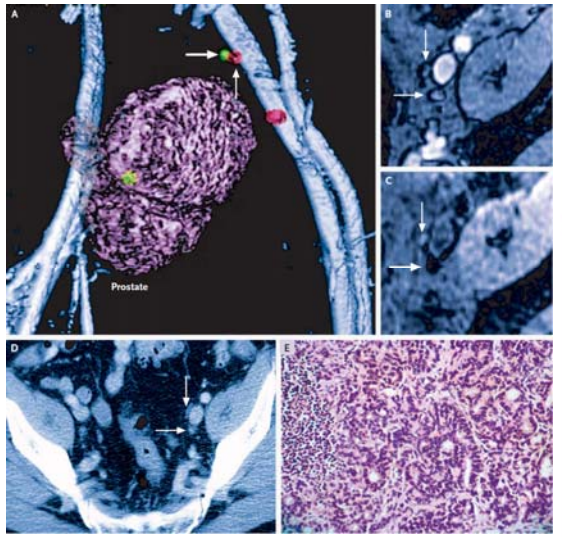
Oesophagus, stomach, bile ducts, ileal/colonic mucosa examined on cell level using fiber optic confocal microscope at autofluorescence emission/excitation wl-s

In vivo real time image of a patient's colonic crypts



Diagnostics-USPIO MRI-A SAD STORY

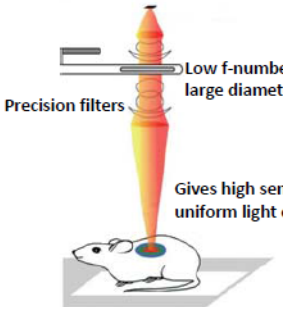




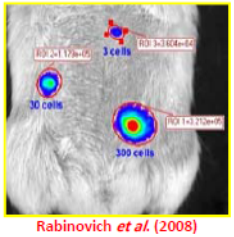
Harishingani M et al N.Engl. J:Med. 2003

BIOLUMINESCENE-The power of nature helping to collect IF-s
Firefly, Jellyfish – TG animals

Cooled (-90C) camera with large CCD chip area for high sensitivity



Resolves multiple bioluminescent reporters
Even detects single cells *in vivo*

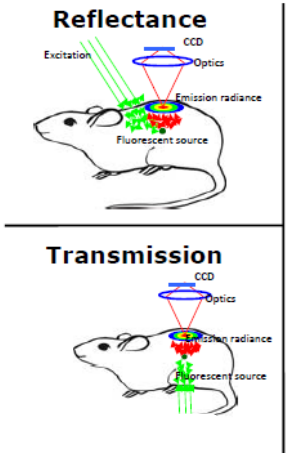


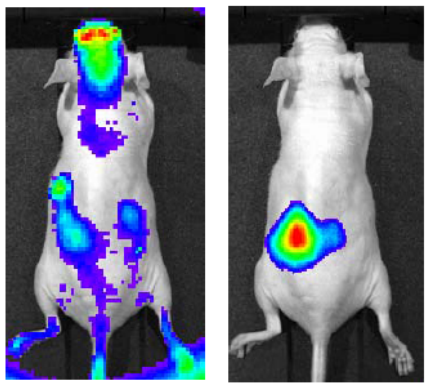
Rabinovich *et al.* (2008)
PNAS 105(38): 14342-6

In vivo imaging of s.c. implanted T cells transduced with optimized firefly luciferase (left) and a 'single' 4T1 breast cancer cell (right)

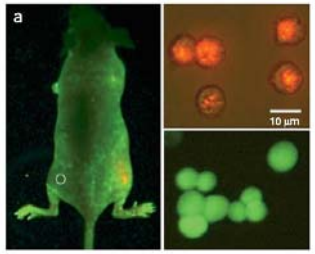
FLUORESCENCE IMAGING

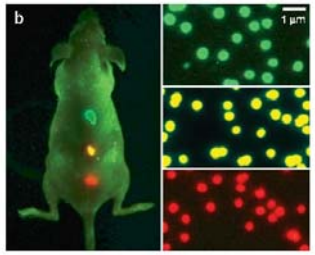
Cooled (-90C) camera with large CCD chip area for high sensitivity and a choice of imaging modes for maximal flexibility, *e.g.*, transmission for deep tissues.

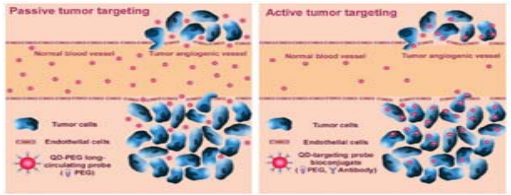




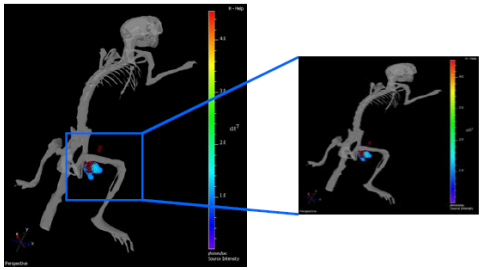
Pillow implanted medial to left kidney, 1x1015 molecules







3D Optical Tomography



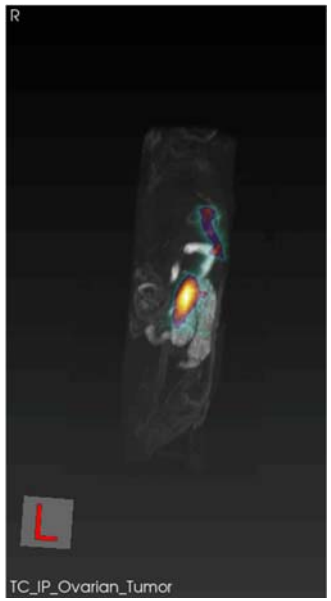
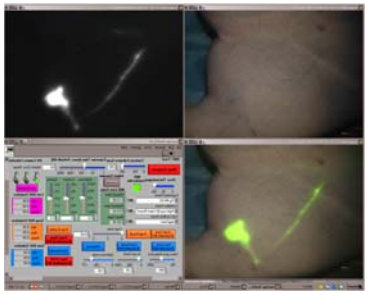
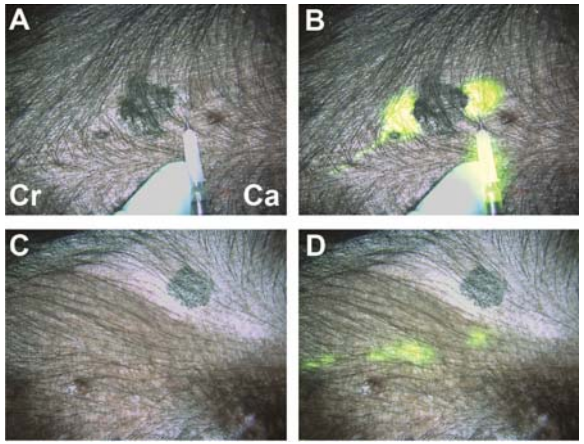


Image guided surgery



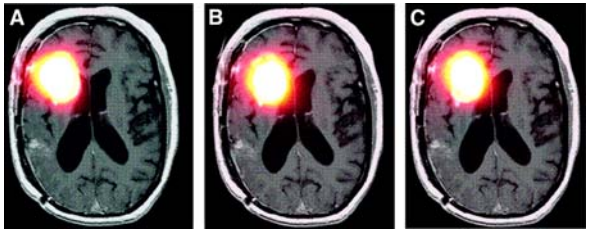
John Frangioni FLARE Harvard

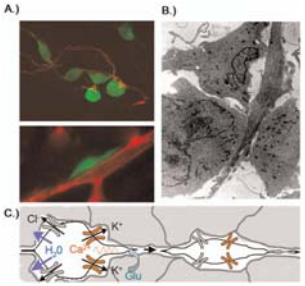
Planar Fluorescence In the Clinic

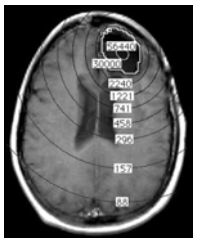


Melanoma, ICG-Albumine particle

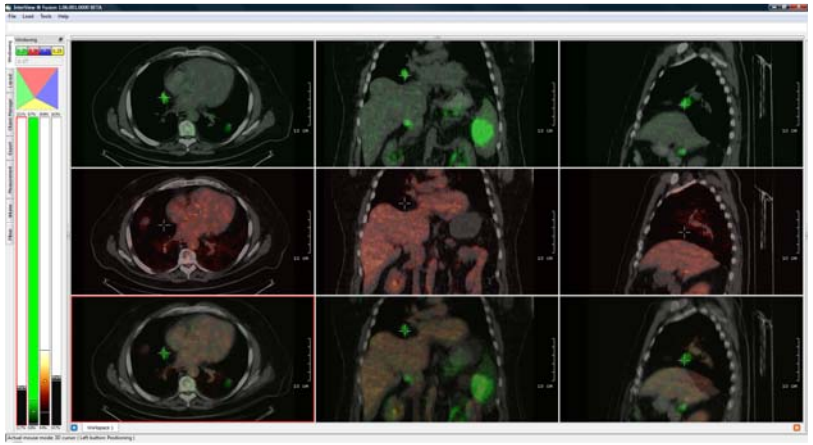
Personalized Targeted Therapy: SPECT/MRI/RNT







Monitoring with FDG-PET

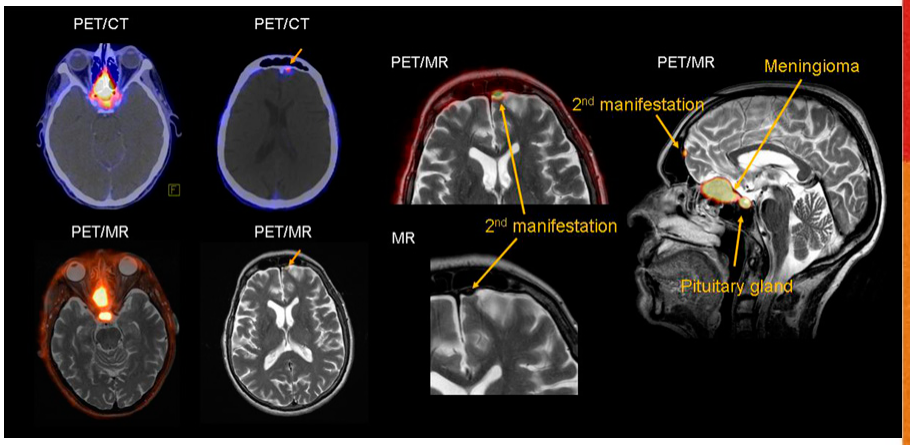


1st PET-CT

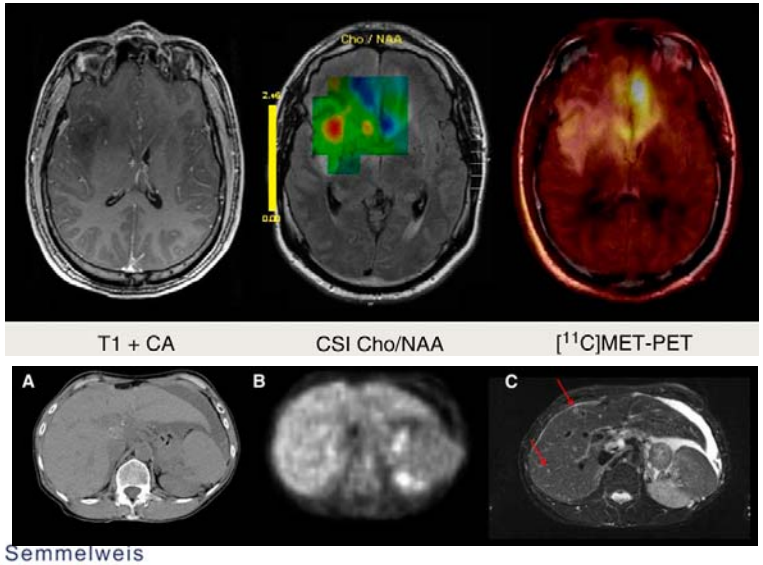
2nd PET-CT

Quadruple fusion

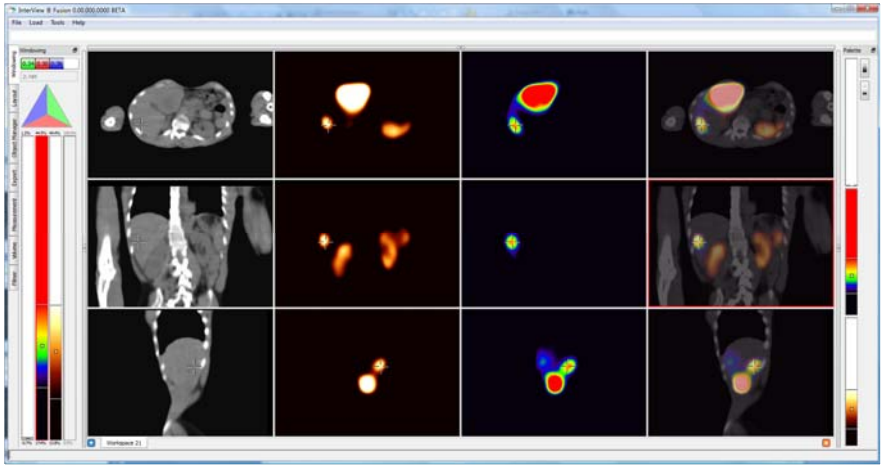
PET/MRI



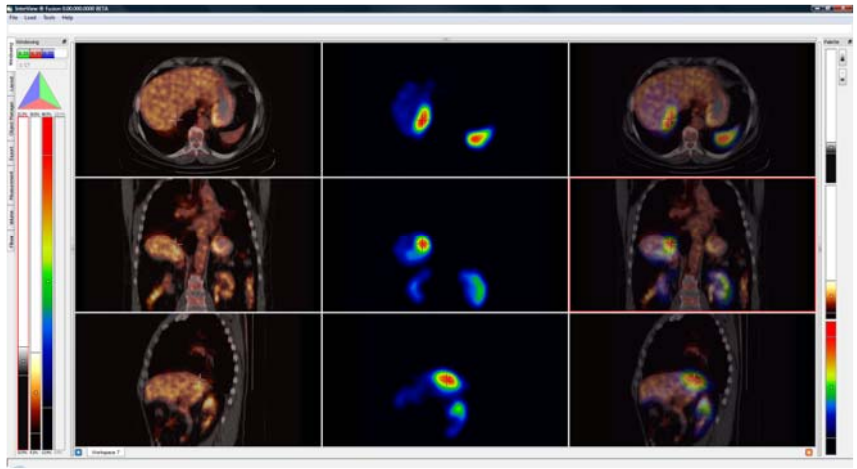
PET/MRI



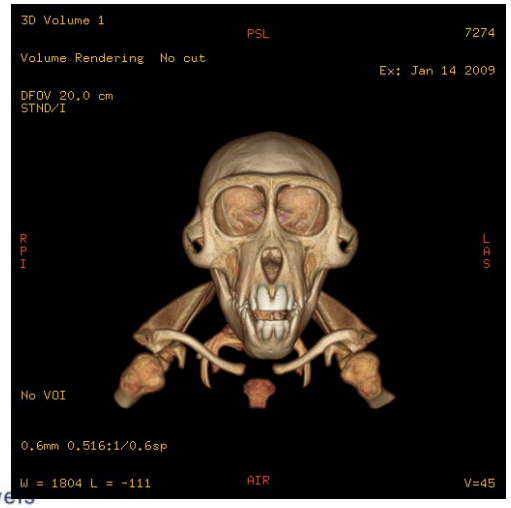
SPECT for neuro-endocrine tumor treatment/assessment



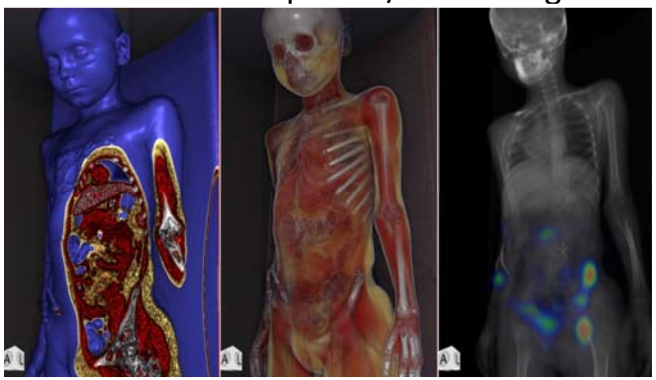
PET/SPECT/CT – Functional and morphological information together



Correlation in Functional/Morph info



SPECT-CT look-up table/windowing



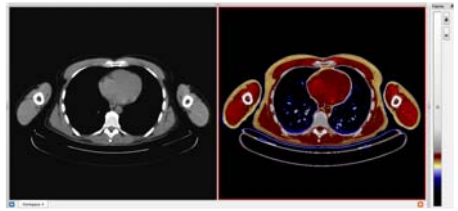
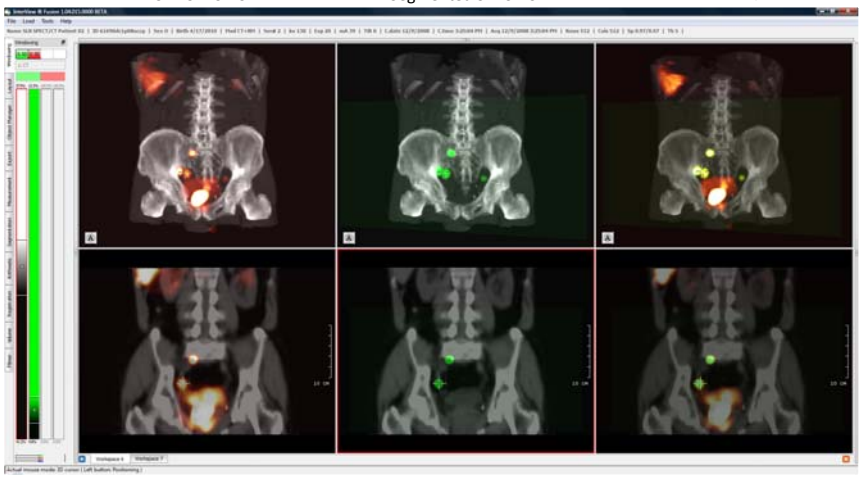
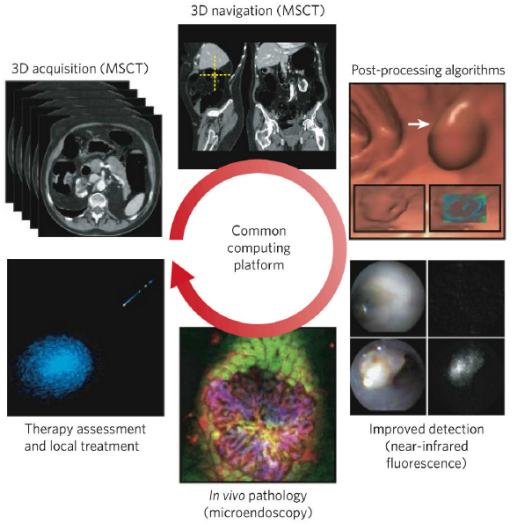


Image segmentation

SLN SPECT-CT | Segmented SPECT-CT | Triple fusion (Segmented SPECT-SPECT-CT)



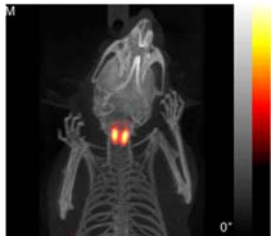
Imaging in Clinical PACS (MGH)



Nanobiotechnológiai és In Vivo Képalkotó Központ

Thanks!

- domokos.mathe@cromedresearch.com



Semmelweis NIVIC

Nanobiotechnology and In Vivo Imaging Center