MOLECULAR IMAGING

Functional Imaging Methods
Multi-Modality

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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)

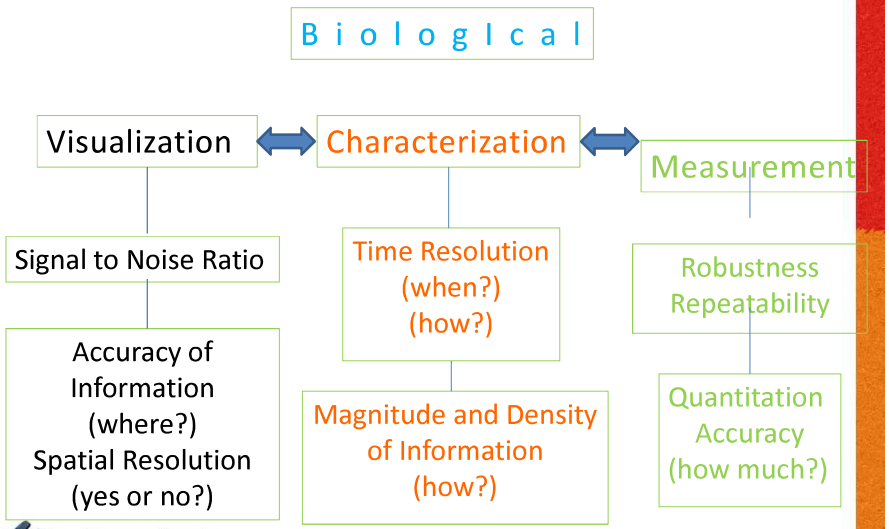
- Correlation of functional and morphological information
- PACS and clinical relevance of image segmentation/registration

- 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:



Molecular Sensitivity

- This quality of any given imaging modality is to be used upon decision of its application

MOLECULAR SENSITIVITY in water" (Levin 2008)=

$$1+(n \cdot N \cdot f \cdot V_{roi} \cdot [S^*k] \cdot t \cdot E_{system})/A \cdot Bgr$$

n: cell concentration
N: number of targeted molecules
f: proportion of the contrast material reaching our target volume to the injected amount
S*k: Specific activity corrected for decay
t: time
E: detection efficiency
V: Volume of our Region of Interest
A: Injected activity
Bgr: Background activity

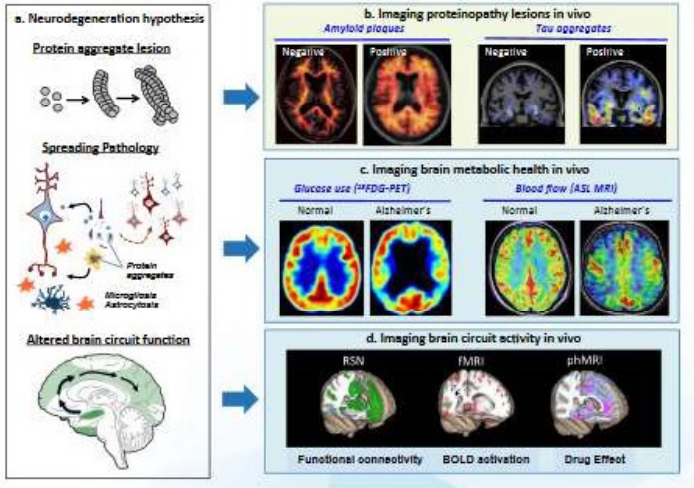
BUT….How all this can be interesting for a Medical Student?

Drug Development

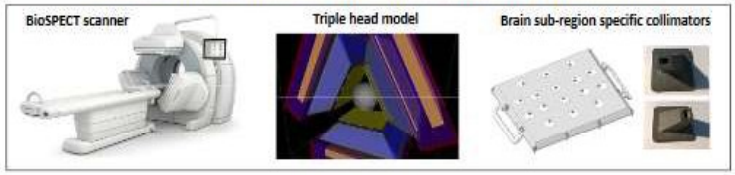
Drug development: How to increase probability of success

- **Begin with disease-relevant biology**
- **Obtain rapid, robust human proof of concept (POC)**
  - De-risk late stage development costs
  - Pursue anti-sense oligonucleotide (ASO) or antibody approaches if target is amenable
- **Develop biomarker capabilities to overcome key challenges**
  - Biological (genetic) heterogeneity
  - Clinical heterogeneity
  - Inability to measure target engagement or the desired biological response
  - Inadequate measurements of disease progression

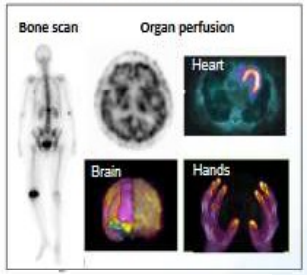
Biogen is de-constructing neurodegeneration using molecular and functional neuroimaging



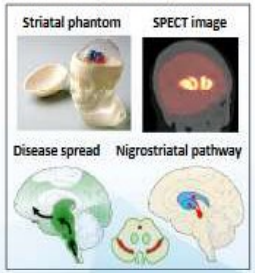
Novel scanner features for brain specific imaging applications



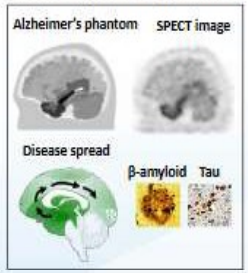
Body and head apertures



Striatum-specific aperture



Cortex-specific aperture



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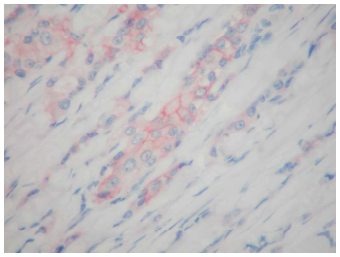
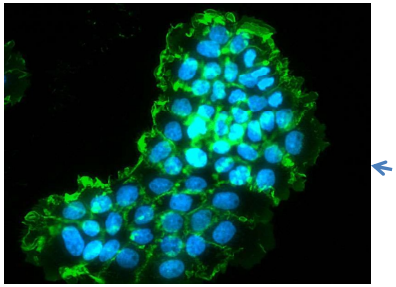
Microscopy: Immunohistochemistry, immunofluorescence

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

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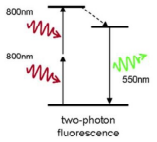
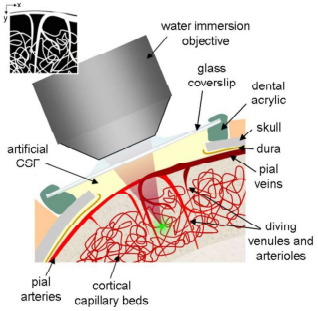
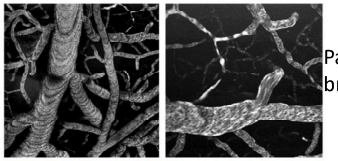
High definition methods in live animals: in vivo dual photon microscopy

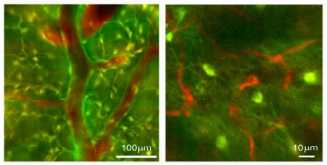
better S/N ratio
increased resolution



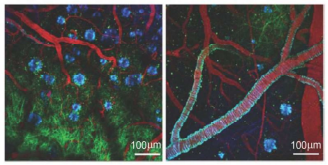




Pattern of RBC flow in brain vessels



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



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

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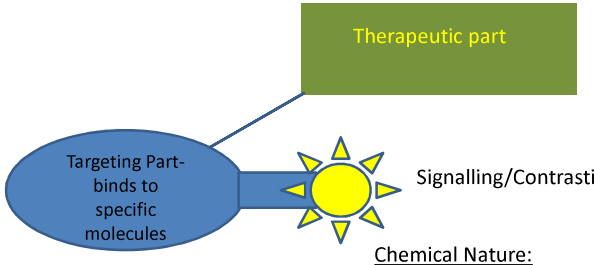
General Structure of a Molecular Probe



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

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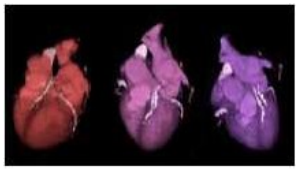
Modalitás	Előnyei	Hátrányai	Fontos kontrasztanyag/jel	Klinikai alkalmazás példái
CT	Any image depths Good time resolution Perces kép-idők Közepesen drága Anatómiai módszer	Sugárterhelés Rossz lágyszöveti kontraszt Jelenleg csak anatómiai és funkcionális képalk.	Ba, I, Kr, Xe	Tumor perfúzió,
PET	Bármilyen mélységű kép Egésztest-képalkotás Kvantitatív mérések Kombinálható CT/MRI-vel	Sugárterhelés Drága Milliméteres felbontás Hosszabb képidő (perc-óra)	C-11, F-18, Ga-68, Cu-64, Zr-89	FDG-PET tumor staging, különböző betegségek diagnosztikája
SPECT	Bármilyen mélységű kép Egésztest-képalkotás Kvantitatív mérések Multiplex Teragnosztika Kombinálható CT-vel	Sugárterhelés Szubmilliméteres-milliméteres felbontás Hosszabb képidők	Tc-99m, I-123, In-111, Lu-177	Molekuláris diagnosztika Radioterápia (NHL, NET, pm. cc.)
MRI	Bármilyen mélységű kép Egésztest-képalkotás Nincs ionizáló sugárzás Kitűnő lágyszöveti kontraszt	Drága Hosszú képidők Korlátozott érzékenység	Gd^{3+}, vas-oxid részecskék (SPIO, USPIO)	Prosztata daganat nycs. met. Fokális májléziók Szív perfúzió
MRS	Nincs ionizáló sugárzása Egésztest-képalkotás	Drága Hosszú képidők Kis érzékenység	Kolin, laktát, kreatin, lipidek, N-acetil-aszpartát	Agytumorok anyagcseréje Alzheimer-kór követése
UH	Nincs ionizáló sugárzás Rövid/valósidejű képalkotás Nagy térbeli felbontás Olcsóság Nagy érzékenység	Egésztest-képalkotás nincs Kontrasztanyagok csak az érrendszerre Operátor-függő	Mikro-buborékok	Fokális májléziók, echokardiográfia, Tumor perfúzió
Optikai módszerek	Nincs ionizáló sugárzás Rövid/valósidejű képalkotás Nagy térbeli felbontás Olcsóság Nagy érzékenység, kvantitatív Multiplex	Korlátozott áthatolóképesség (1 cm) Nincs egésztest-képalkotás	Fluoreszcens molekulák és festékek, fény-elnyelő nanorészecskék	OCT-érelmeszesedés, retinopathiák, kolonoszkópia

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



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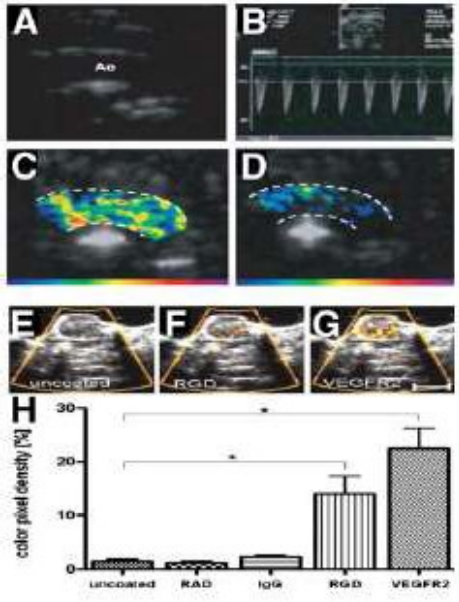
UltraSound	3D differences in echo and spreading of sound waves
Advantages	No ionizing radiation Fast/RT imaging High Sensitivity High Resolution Cheap
Disadvantages	No WB img. Only vascular contrast materials Operator dependency
Contrast Materials	Micro-Bubbles
Clinical Use	Focal liver lesions, Echocardiography,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



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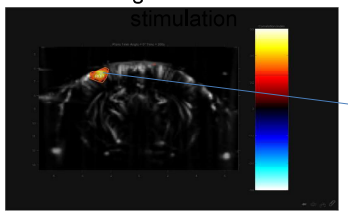
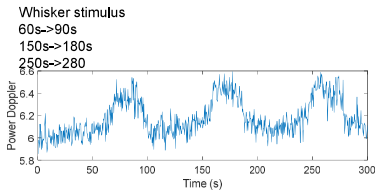
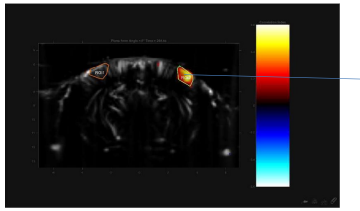
Ultrahigh Resolution Ultrasound Doppler Microscopy
Mouse brain blood flow images – Human Cardiac Images

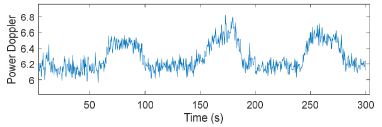
Right whiskers stimulation





Left whiskers stimulation





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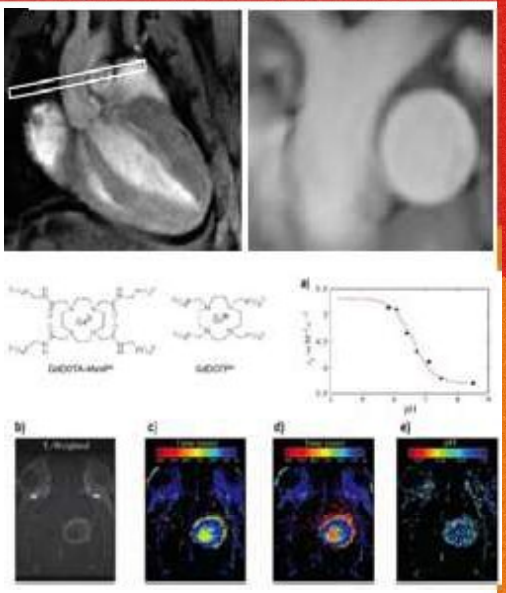
MRI (IRM…)	3D / 2D Image of Proton Spins
Advantages	Any Imaging Depth and Plane WB Imaging No ionizing radiation High Soft Tissue Contrast
Disadvantages	Expensive Low Sensitivity Long imaging time
Contrast Materials	Gd3+, iron-oxide particles (SPIO, USPIO)
Clinical Use	Liver, Brain Lesions, Cardio-MRI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



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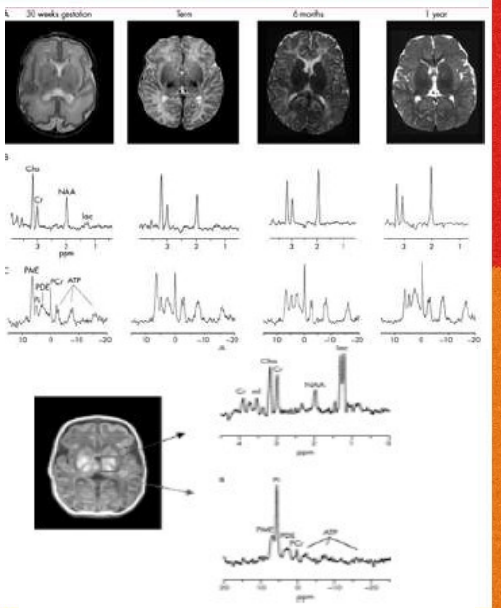
MRS	Recorded Electromagnetic Resonance Spectrum
Advantages	No ionizing radiation WB Imaging
Disadvantages	Expensive Very low sensitivity External Calibration / Special Knowledge
Contrast Materials	Cholin, Lactate, Creatin, Lipids, N-Ac-Aspartate
Clinical Use	Brain Tumor Stratification, Stroke
Voxel Sizes,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



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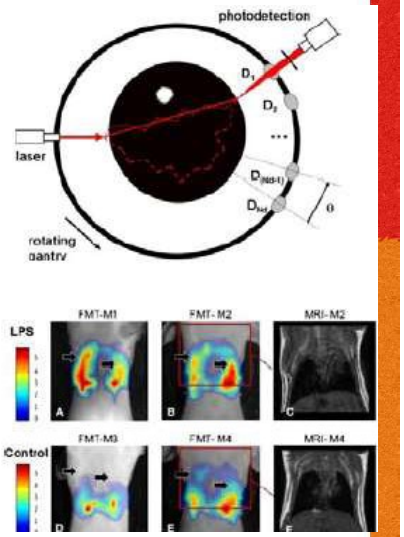
Optical Methods	Visible/NIR Light Transmission/Reflectance/Emission/ Scatter in 2D , 3D
Advantages	No ionizing radiation Short/RT Imaging High Spatial Resolution Very Sensitive, Semi-Quantitative Multiplex
Disadvantages	Limited Transparency No WB imaging
Contrast Materials	Fluorescent molecules, Light-emitting 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



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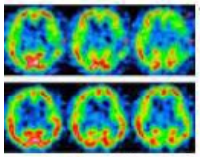
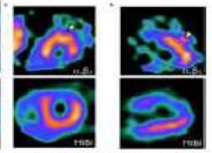
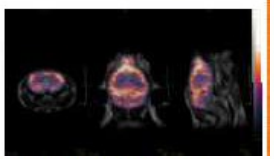
SPECT	3D Gamma-ray Source Array in Tissue
Advantages	Any imaging depth WB Imaging Quantitative Good resolution Multiplexing Theragnostics Combination w/CT
Disadvantages	Radiation Dose Sub-mm Resol. Long imaging times
Contrast Materials	Tc-99m, I-123, In-111, Lu-177, Ho-166, Tl-201
Clinical Use	Nuclear 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



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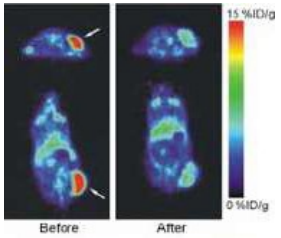
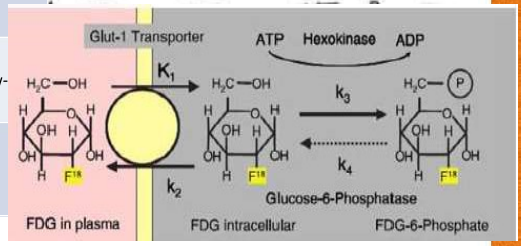
PET	3D 511 keV Gamma-ray Source Array in Tissue
Advantages	Any imaging depth WB Imaging Quantitative Anatomical Co-registration CT, MRI
Disadvantages	Radiation Dose PRICE Resolution Longer imaging times
Contrast Materials	C-11, F-18, Ga-68, Cu-64, Zr-89
Clinical Use	FDG Patient Staging+Follow-
Voxel 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





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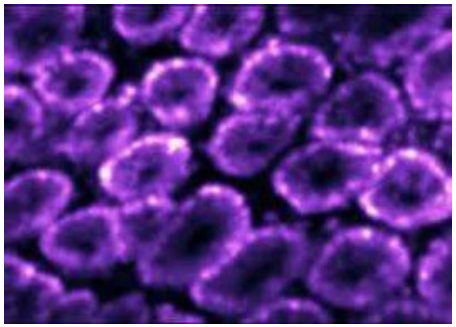
Confocal Laser Endomicroscopy

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



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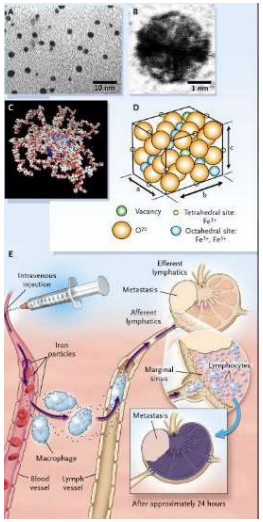
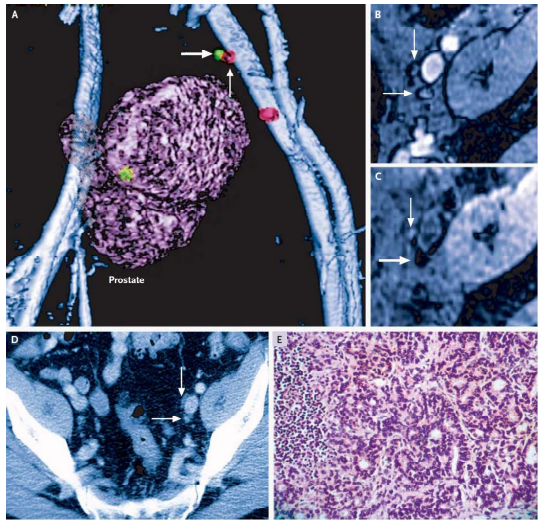
Diagnostics-USPIO MRI





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

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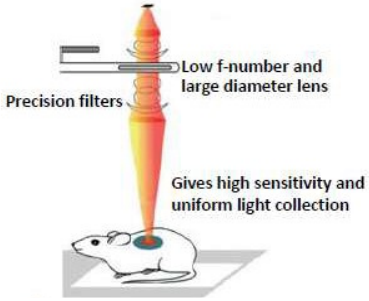
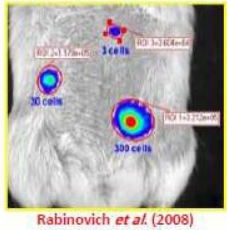
BIOLUMINESCENCE
Energy-dependent multi-event reporter imaing
Firefly, Jellyfish – TG animals

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)

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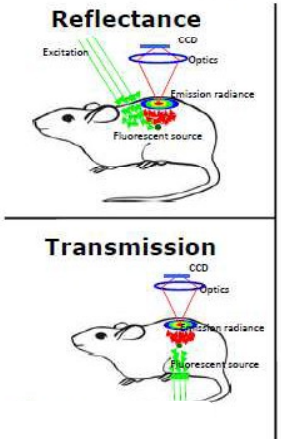
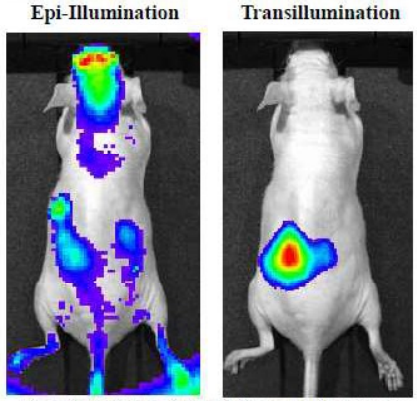
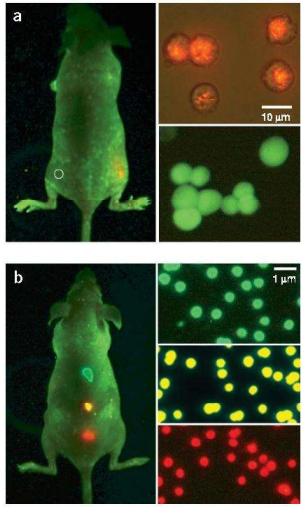
FLUORESCENCE IMAGING

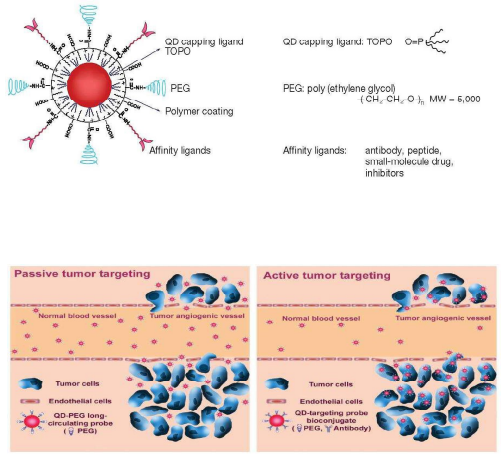
Cooled (-90C) camera with large CCD chip area for high sensitivity and a choice of imaging modes for maximal flexibility, *e.g.*, transmission for deep tissues.



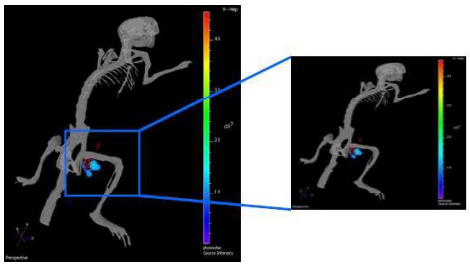


Pillow implanted medial to left kidney, 1x1015 molecules





3D Optical Tomography



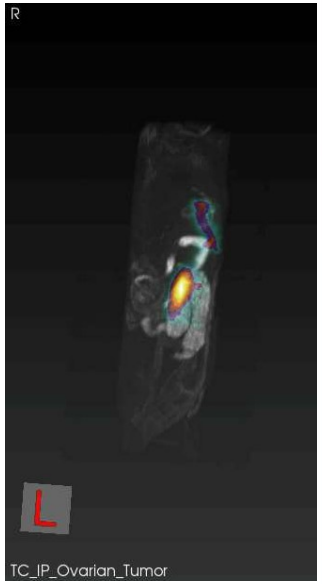
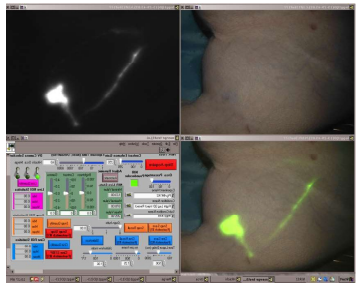
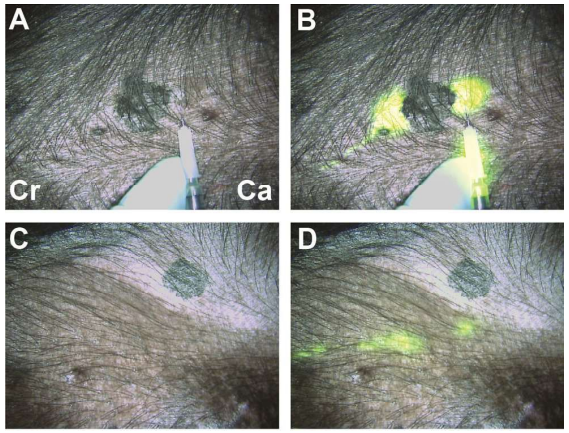


Image guided surgery



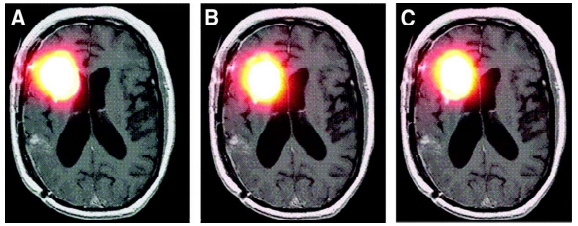
John Frangioni FLARE Harvard

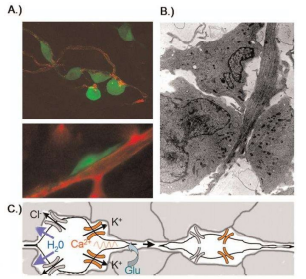
Planar Fluorescence In the Clinic

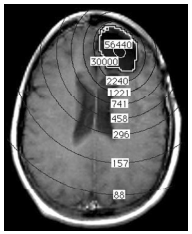


Melanoma, ICG-Albumine particle

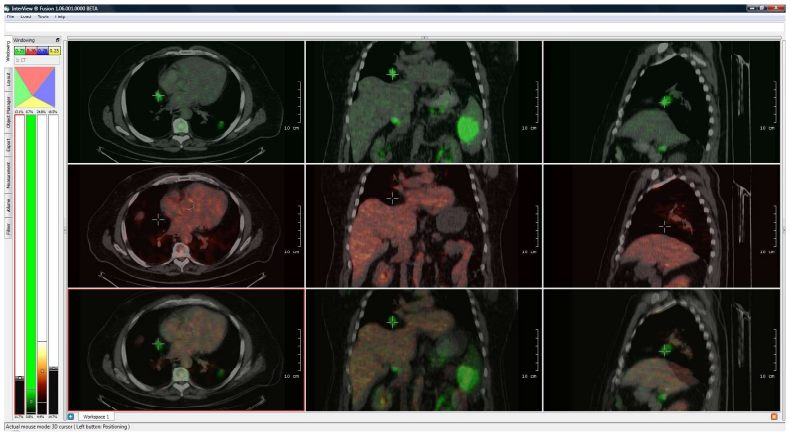
Personalized Targeted Therapy: SPECT/MRI/RNT







Monitoring with FDG-PET

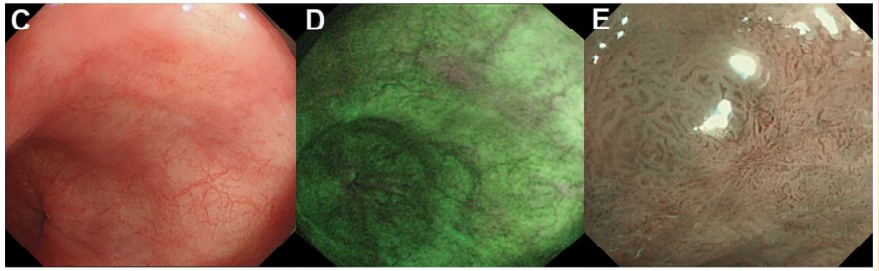


1st PET-CT

2nd PET-CT

Quadruple fusion

Planáris autofluoreszcencia-endoszkópia

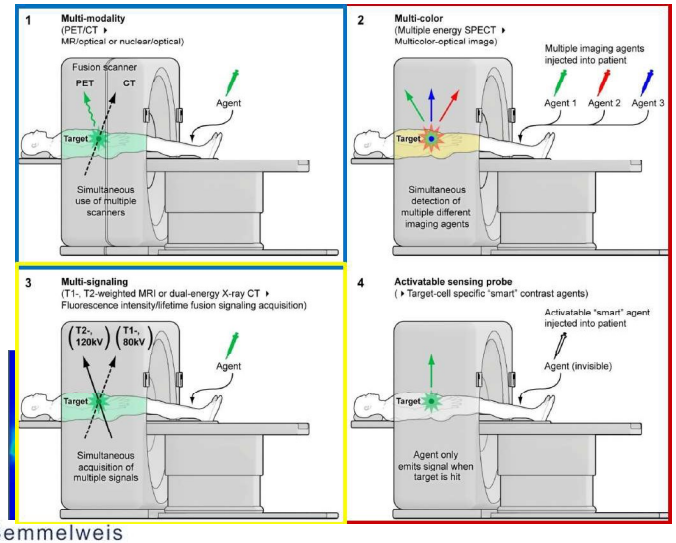


C: Barrett-oesophagus endoszkópia, D: autofluoreszcencia (lila) E: nagyfelbontású endoszkópia-irreguláris mintázat. A biopszia adenocc.-t igazolt.

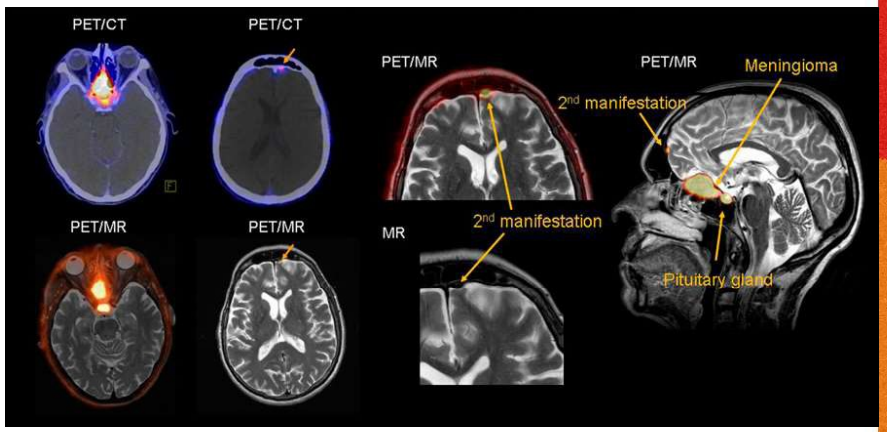
OCT (optical coherence tomography)

- Retina:
- Mucosae
- Cartilage
- Blood Flow
- Mm penetration
- Micron resolution
- Real time imaging

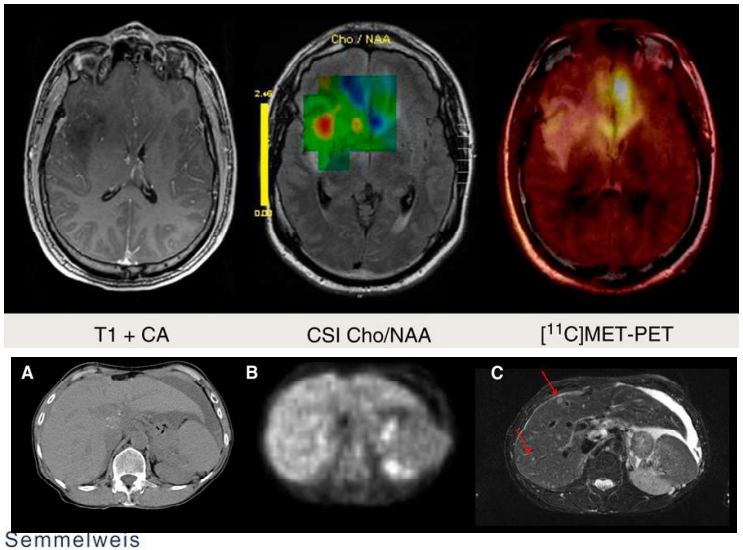
Multimodális rendszerek lehetőségei



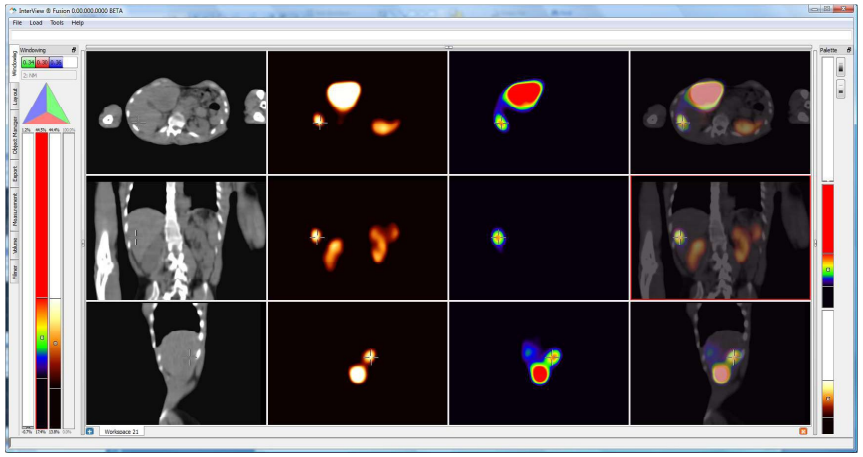
PET/MRI



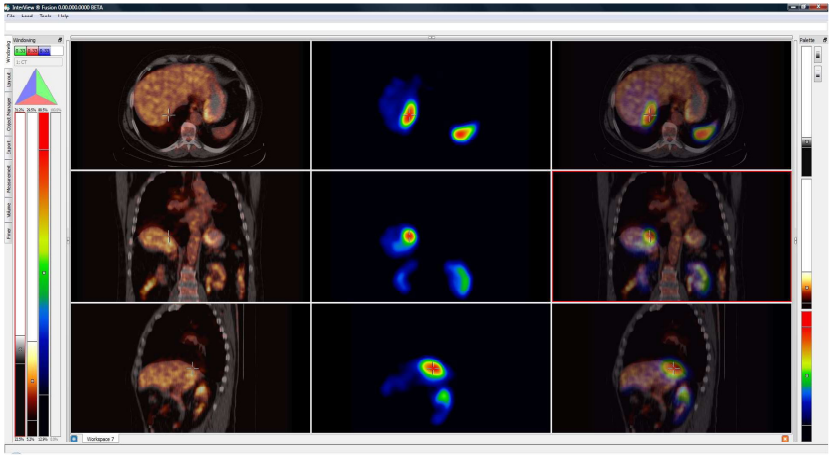
PET/MRI



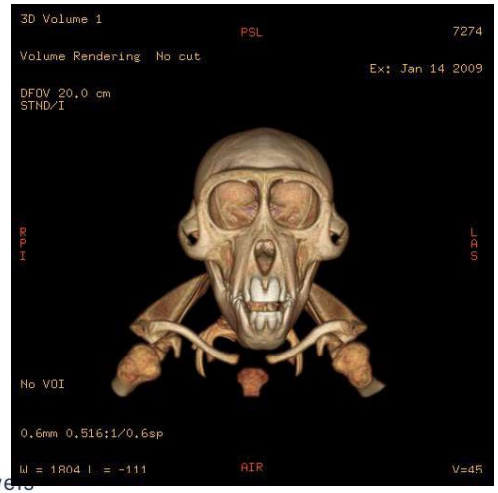
SPECT for neuro-endocrine tumor treatment/assessment



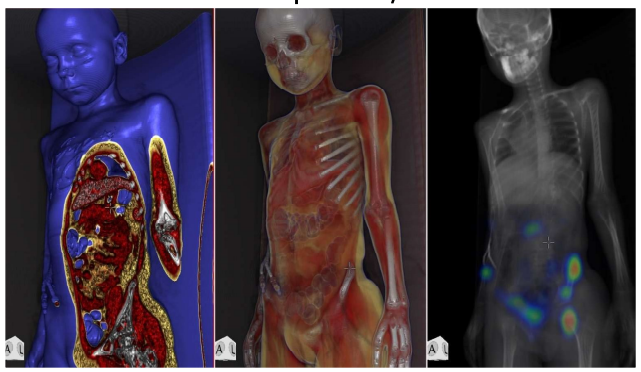
PET/SPECT/CT – Funkcionális és morfológiai információ együtt

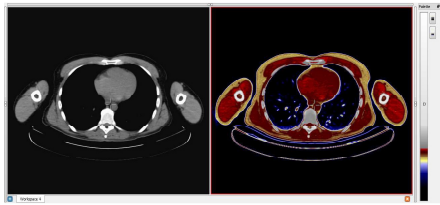


Correlation in Functional/Morph info



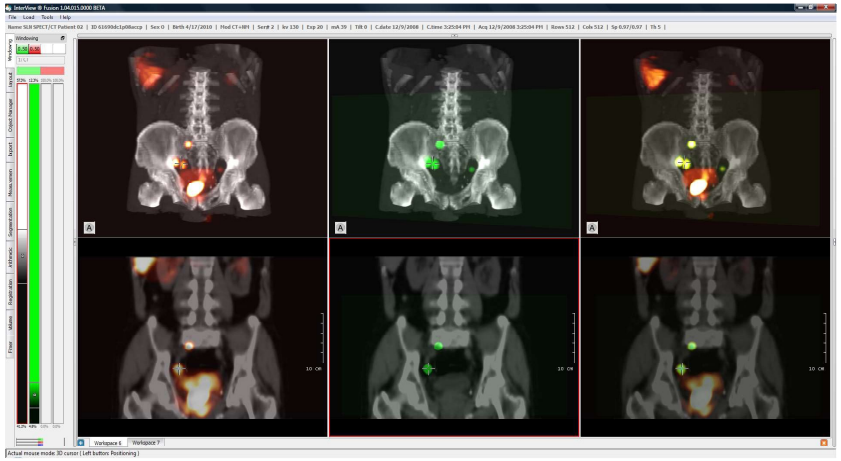
SPECT-CT look-up table/ablakolás



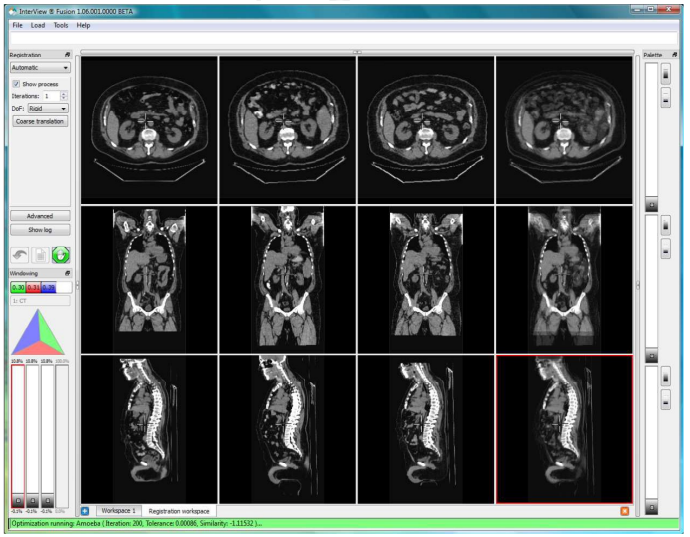


Képszegmentáció

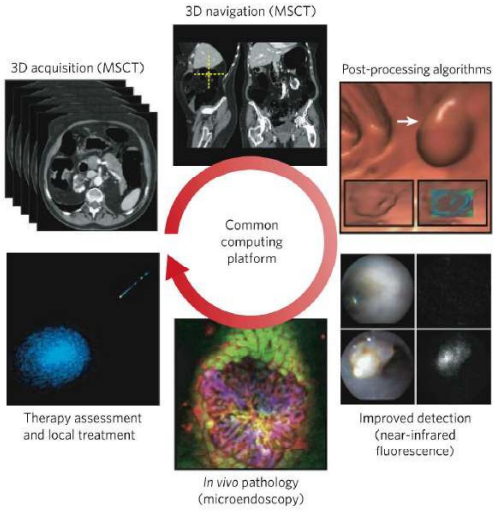
SLN SPECT-CT | Segmented SPECT-CT | Triple fusion (Segmented SPECT-SPECT-CT)



Képregisztráció



Imaging in Clinical PACS (MGH)



Thanks!

- domokos.mathe@cromedresearch.com