Chimica & Imaging Molecolare :

nuovi percorsi per una diagnostica innovativa

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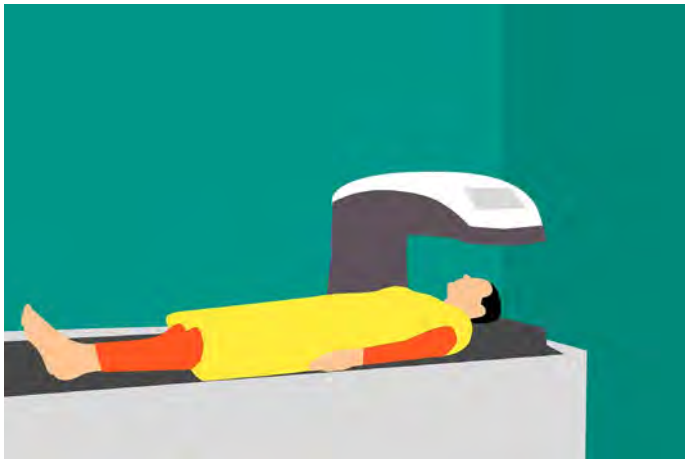
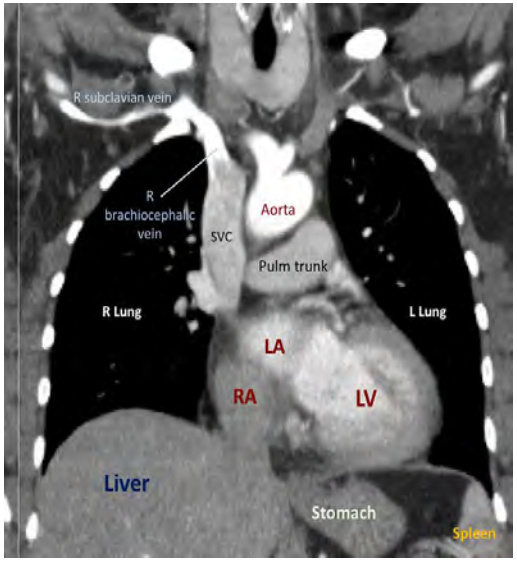
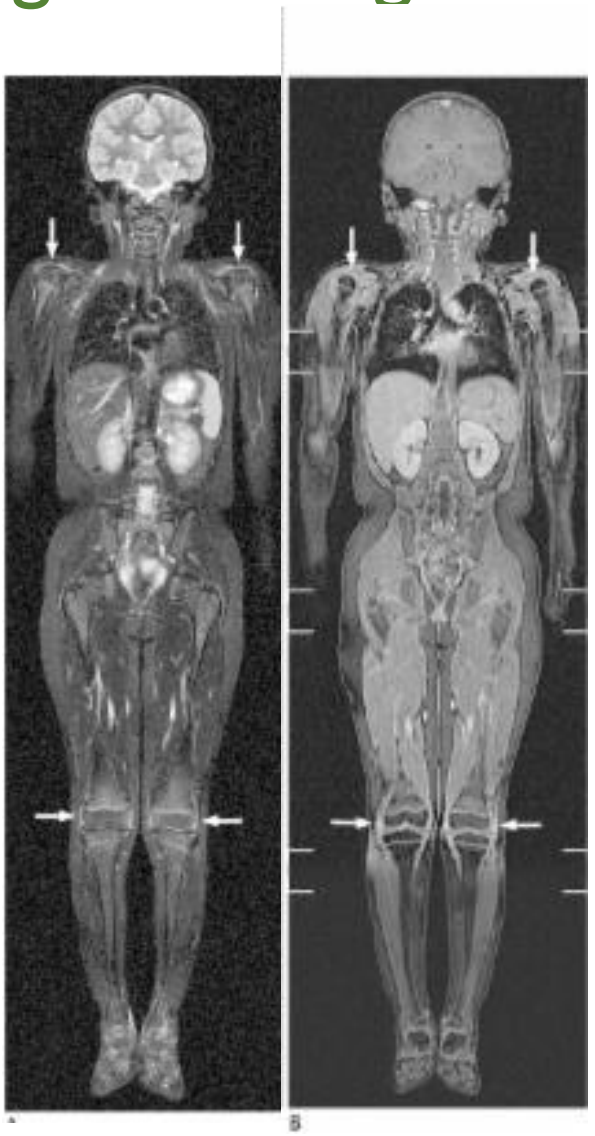
Great progress in the field of Imaging Technologies



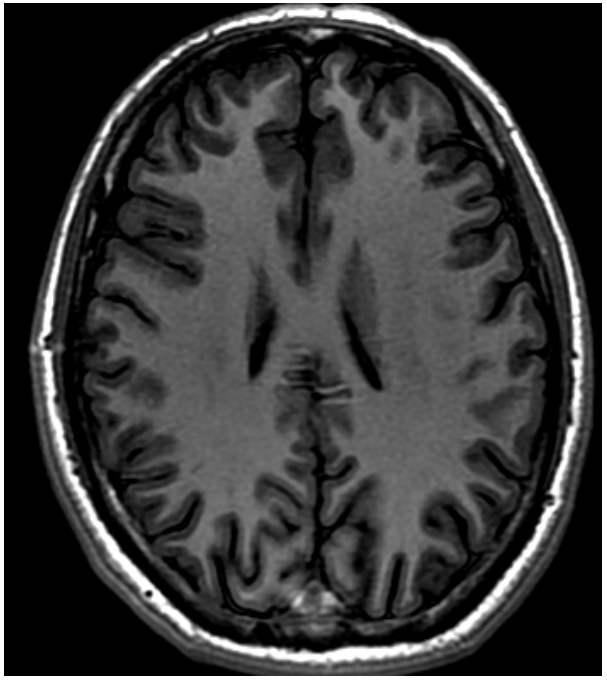




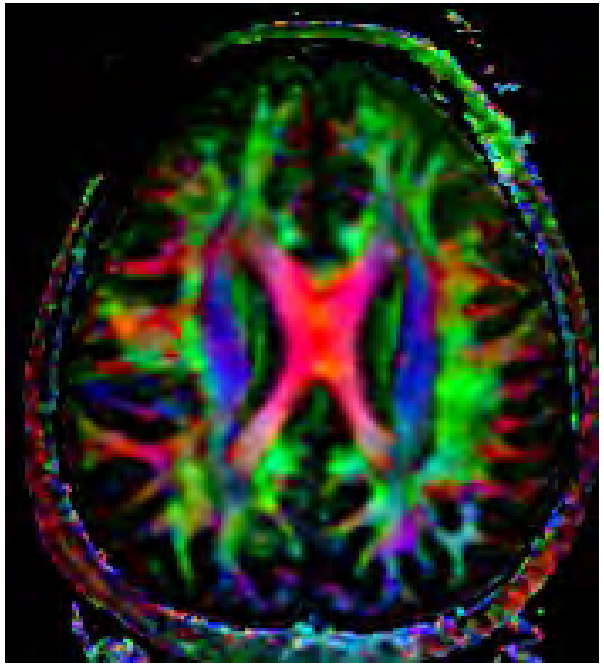
Computed Tomography

Magnetic Resonance

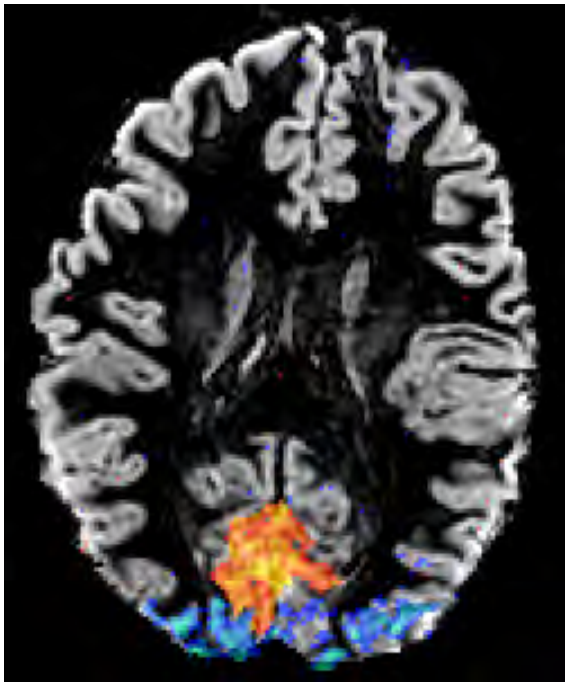
MRI of the Brain



Anatomy



Connectivity



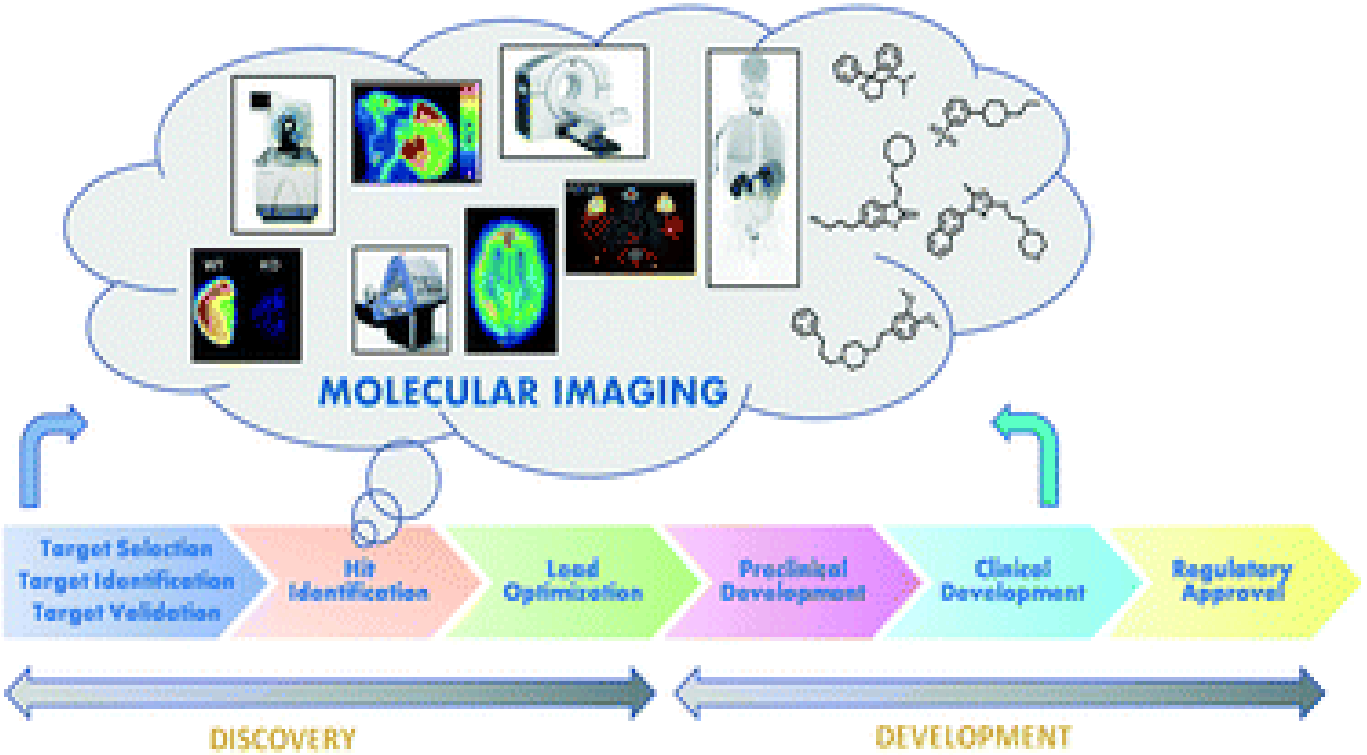
Function

Molecular Imaging

- Develop molecular probes & contrast agents
  - links imaging modality with specific biological processes
- Image specific molecular targets
  - capitalize on mapping of human genome
- Drug development
  - monitor drug delivery, validation & efficacy, effects on biological target

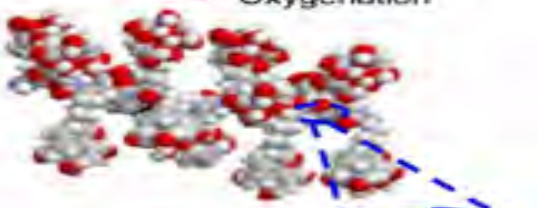
The practice of Medical Imaging in the era of Molecular Medicine

Diagnostic agent basics: molecular imaging



New Molecular "Targets"...

- Cell Surface Receptors
- Antigens
- Gene Expression
- Proteins
- Enzymatic Activity
- Chemical Comp.
- Metabolism
- Oxygenation



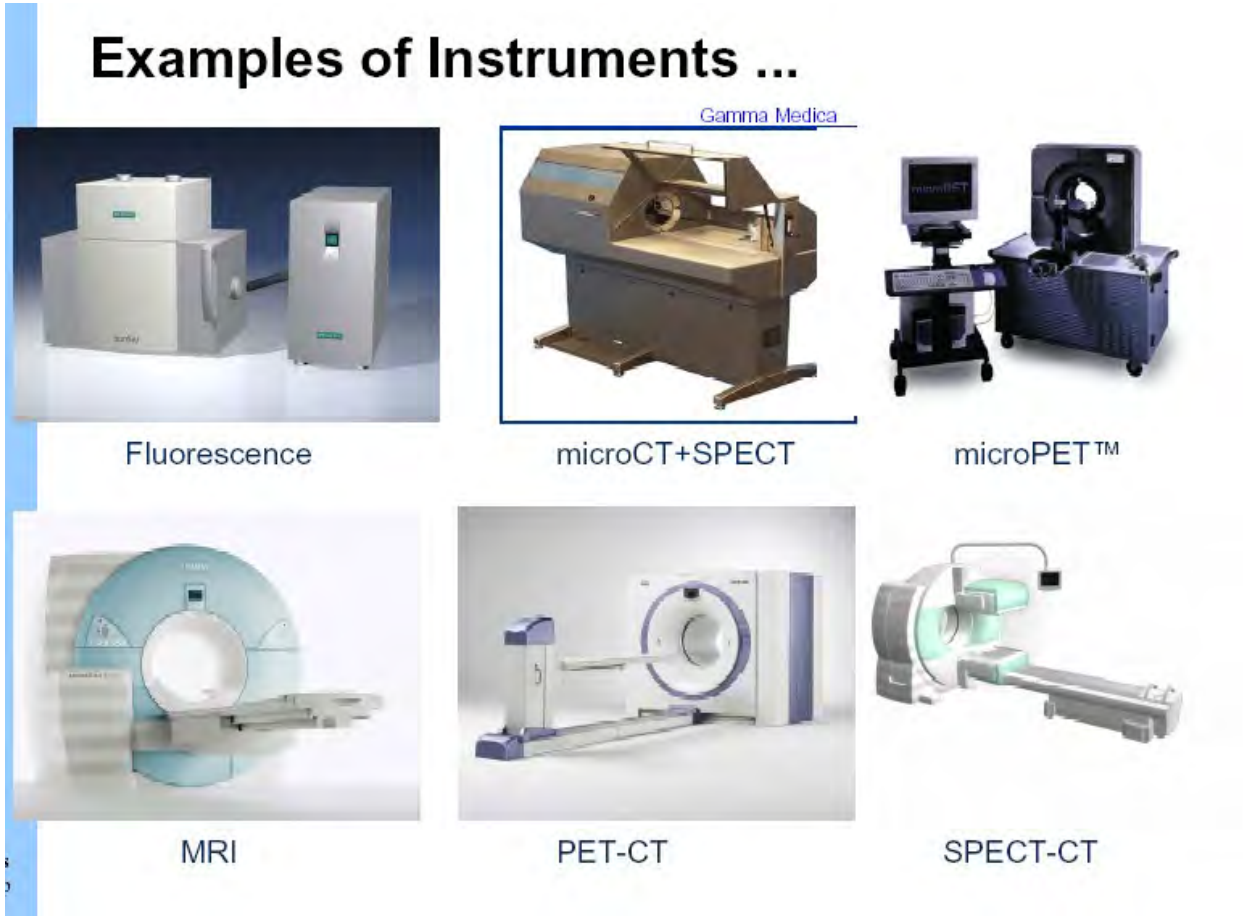
... Require New Diagnostic Science

- **Target Analysis & Identification**
- **Novel Targeting Agents**
- **Payloads** – Imaging "Flares" or Therapy "Smart Bombs"

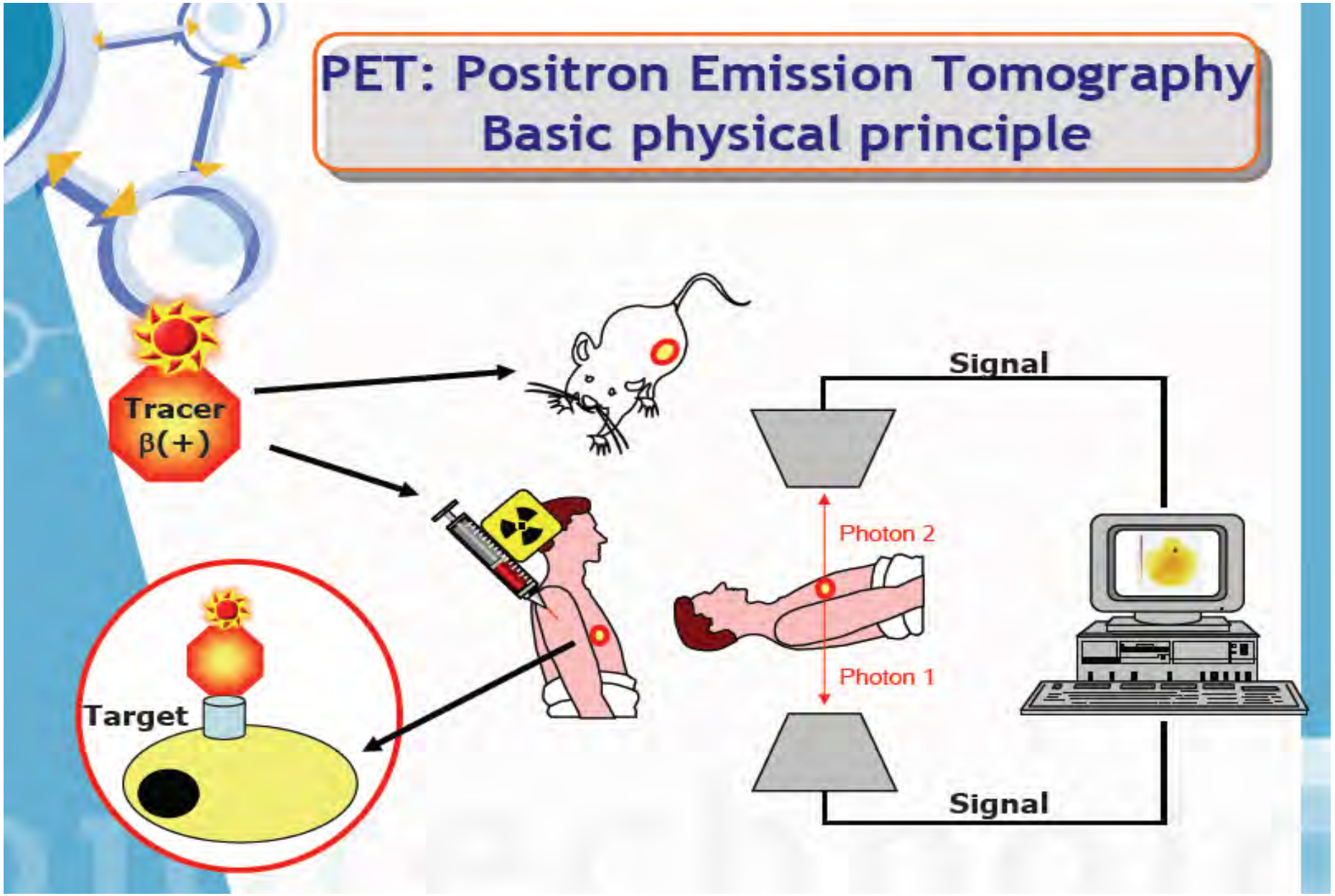
Huge Opportunity and Challenges

Imaging Modalities

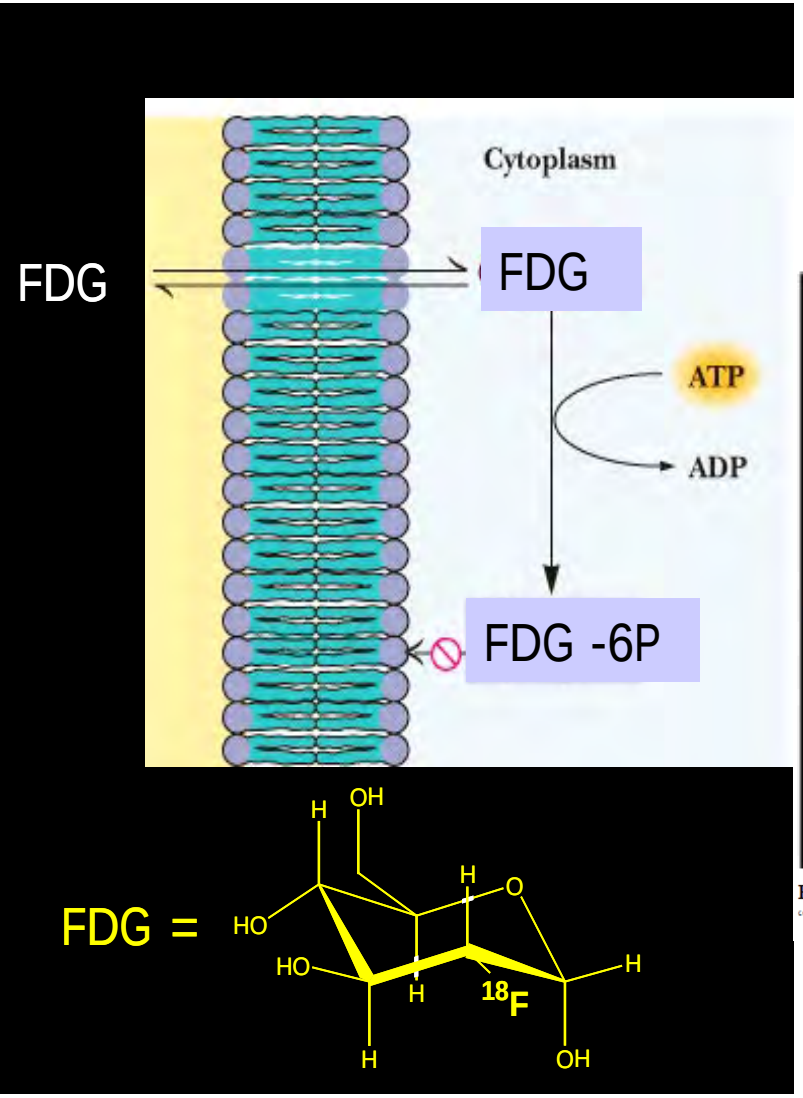
- Nuclear Medicine (PET, SPECT)
- Magnetic Resonance (MRI)
- Computed Tomography (CT)
- Ultrasound
- Optical Imaging



PET & Molecular Imaging



FDG/PET (fluorodeoxyglucose positron emission tomography)



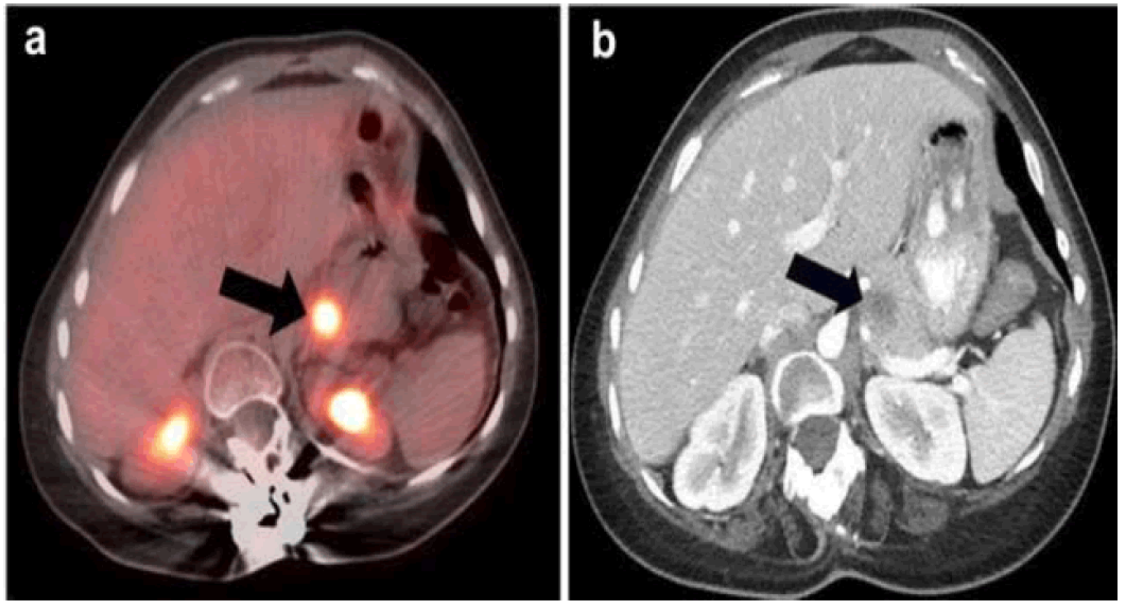
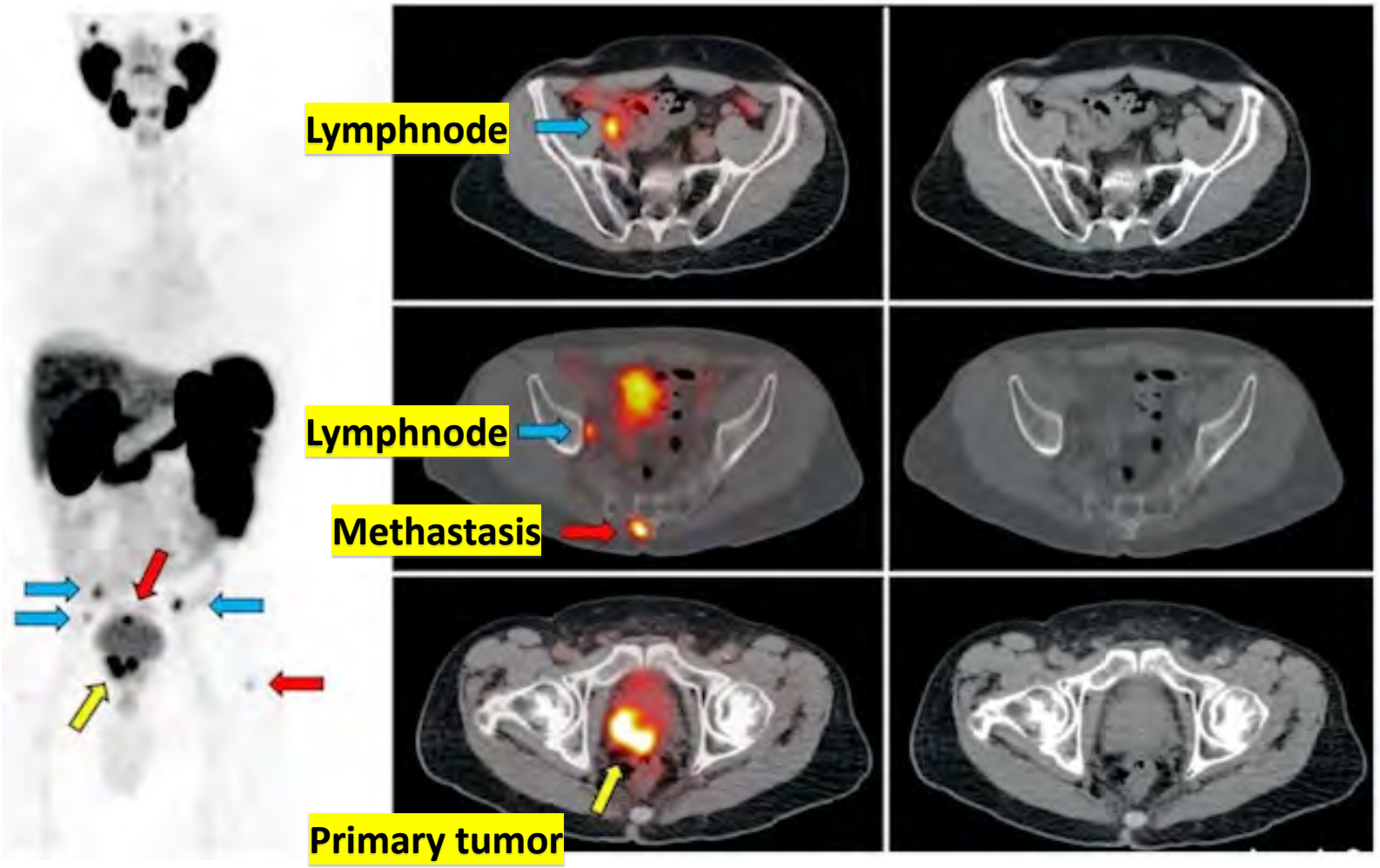
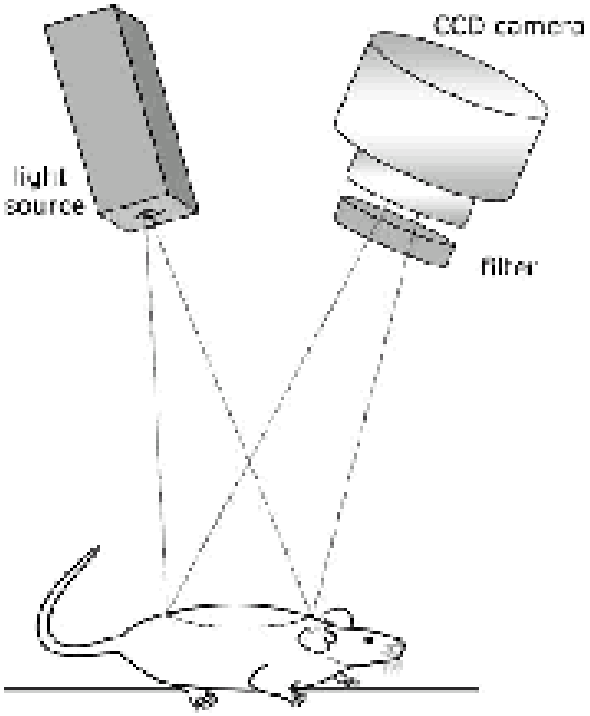


Figure 12. a. Fused axial PET/CT image shows a hypermetabolic lesion of non-Hodgkin lymphoma of the pancreas (arrow). The other two bright "spots" represent normal kidney excretion of FDG tracer. **b.** Corresponding axial CT image (arrow).

Ga-68 PSMA-11 PET/CT images of a patient with prostate cancer.



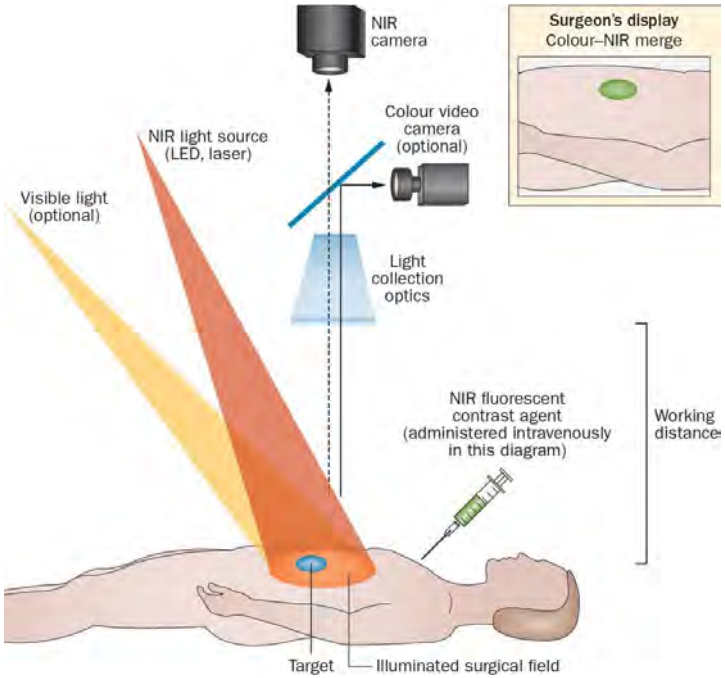
Optical Imaging



- In vivo system for fluorescence reflectance
- High sensitivity
- Drawbacks: penetration of light in biological tissues, autofluorescence
- Very useful in drug development
- The probe are dark in the native state and after enzymatic cleavage of the black-bone carrier they fluoresce when appropriately excited

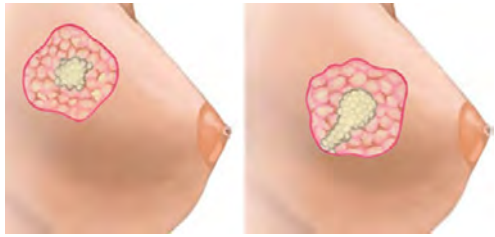
Fluorescence image-guided surgery

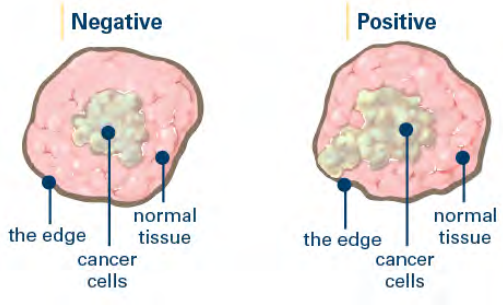
TECHNOLOGY



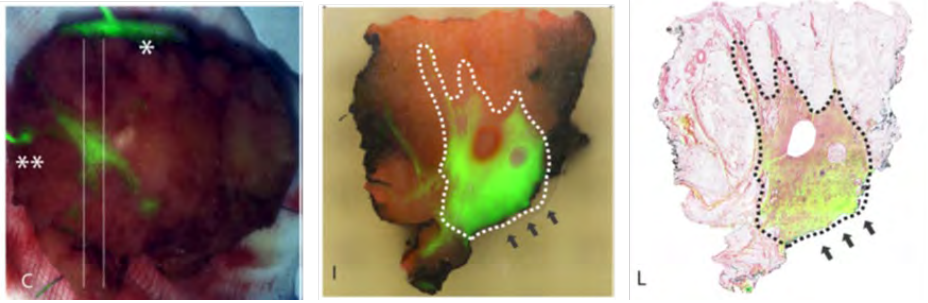
Vahrmeijer et al 2013. Reviews Clinical Oncology. Vol 10. 507–518

MEDICAL NEED





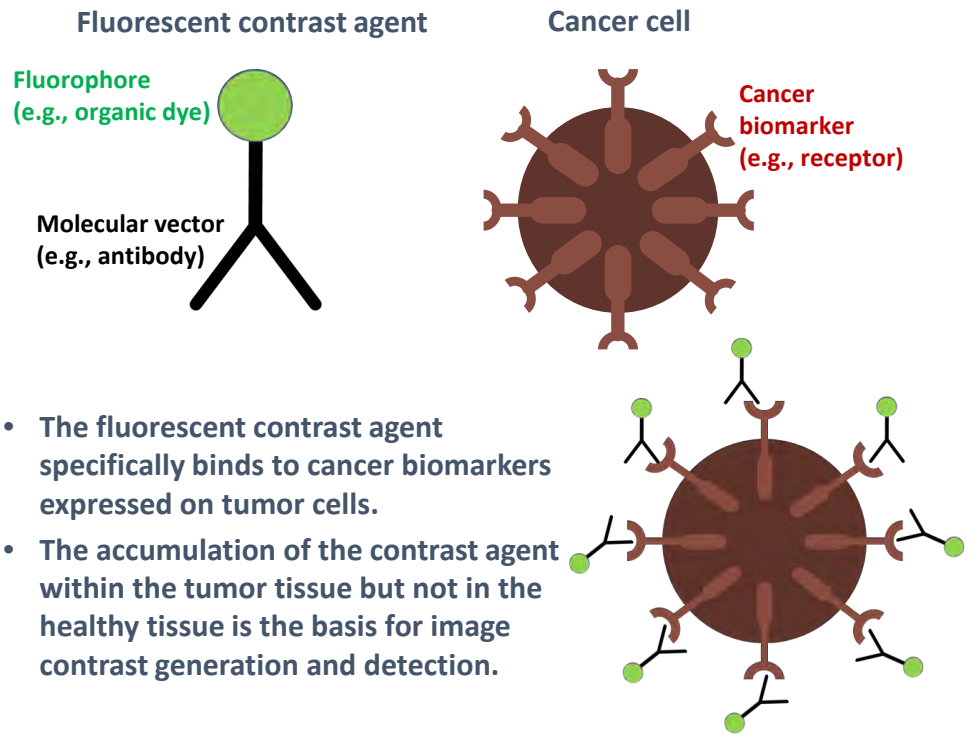
Excised tumor lump | Gross pathology | Histopathology



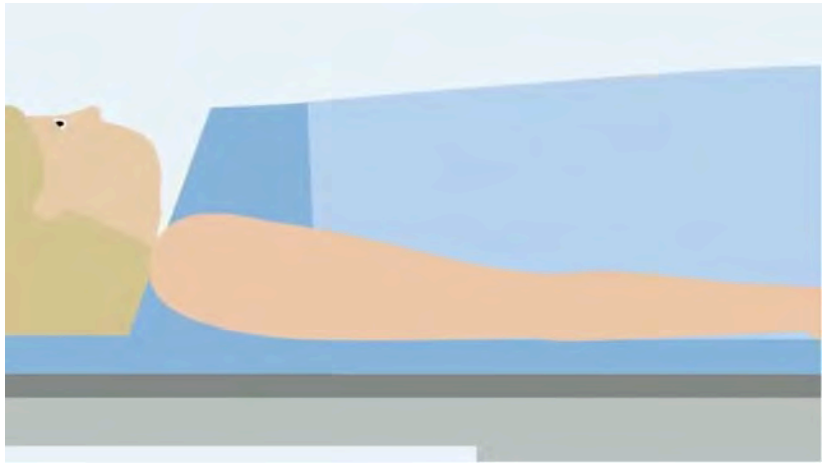
Detection of positive margin on excised breast tumor lump confirmed by histopathology

Lamberts et al., Clin Cancer Res 2016

Fluorescence image-guided surgery

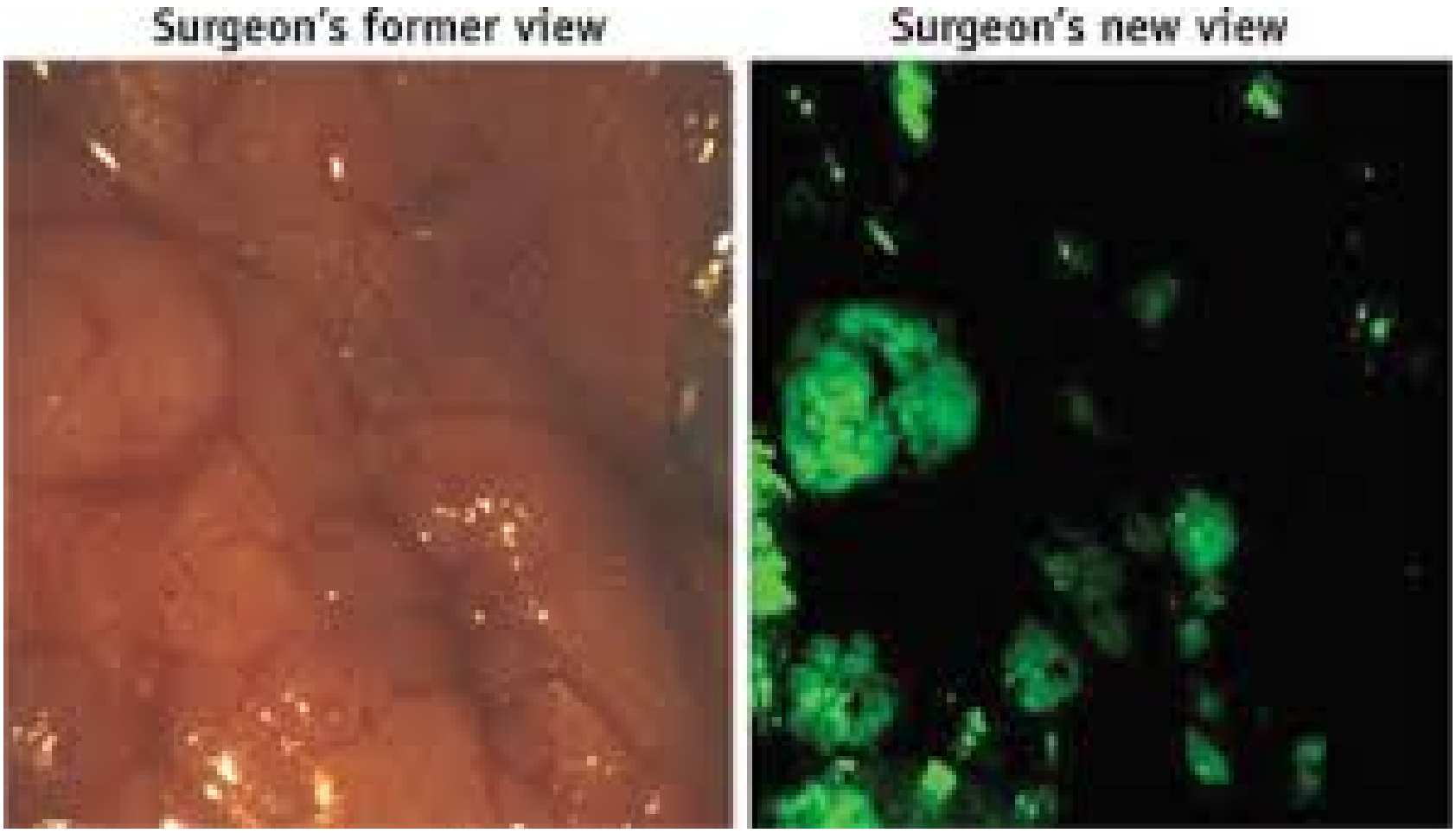


- The fluorescent contrast agent specifically binds to cancer biomarkers expressed on tumor cells.
- The accumulation of the contrast agent within the tumor tissue but not in the healthy tissue is the basis for image contrast generation and detection.

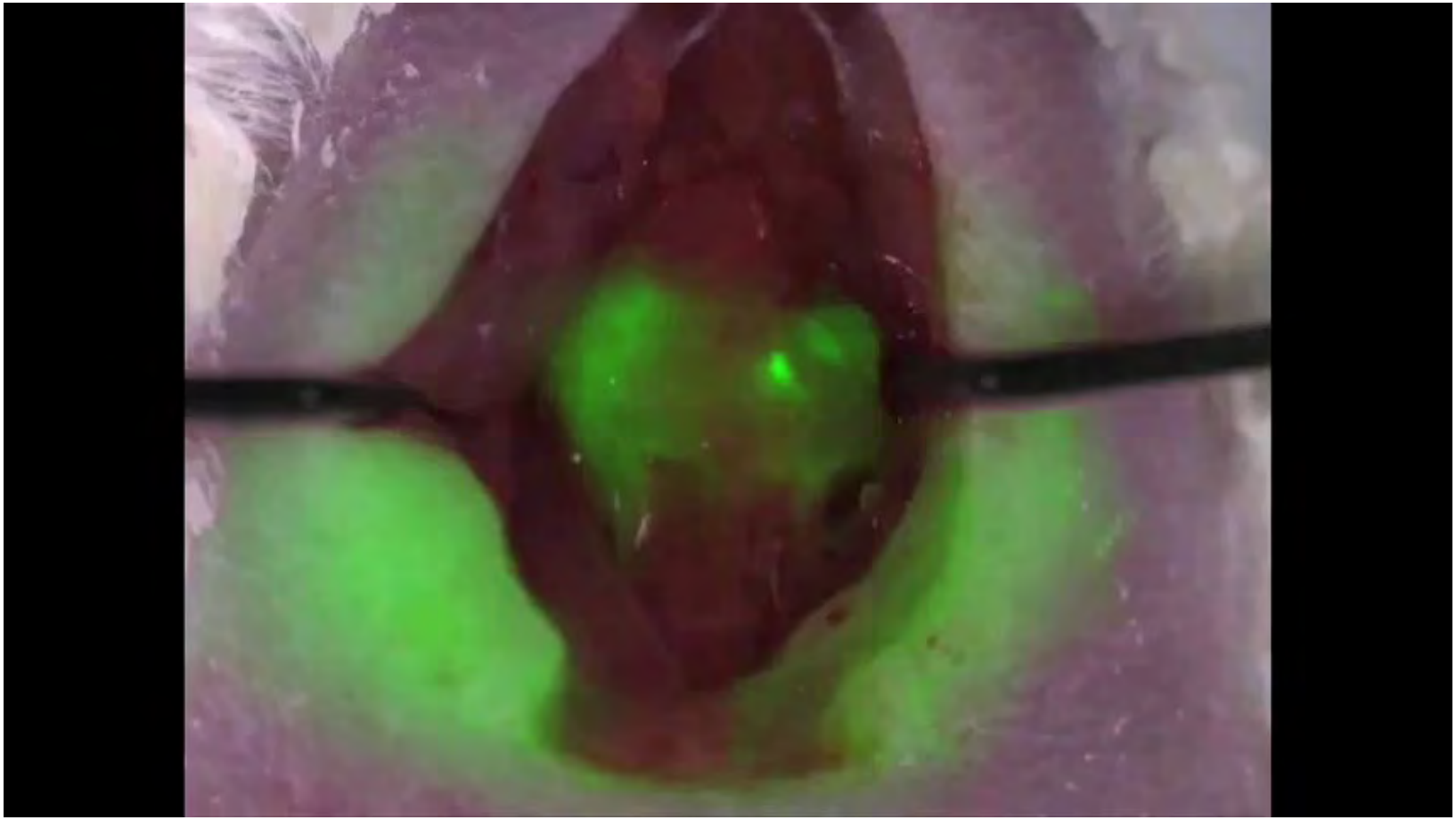


Vahrmeijer group, Leiden (NED)

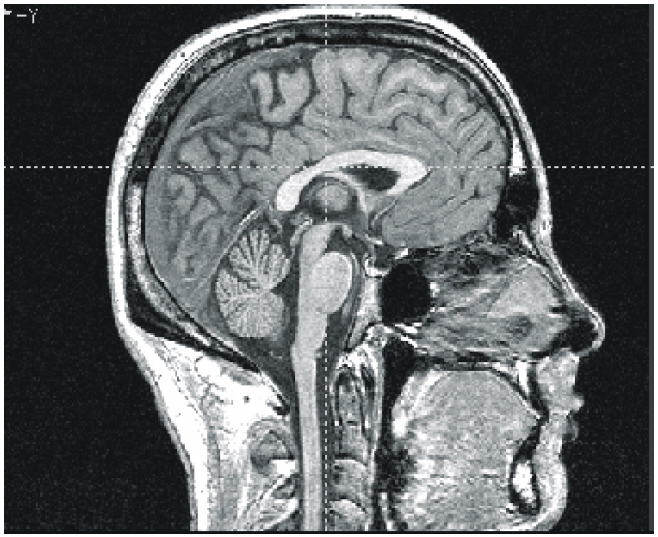
IMAGE-GUIDED SURGERY: Fluorescence-guided multispectral imaging enables excision of minuscule ovarian tumors



Imaging guided surgery by detecting the fluorescent signal from a tumor targeting probe



Magnetic Resonance Imaging (MRI)



MR sagittal image of human head

- **Non-invasive and safe technique**
- **Great spatial resolution (mm scale)**
- **Outstanding diagnostic capability**

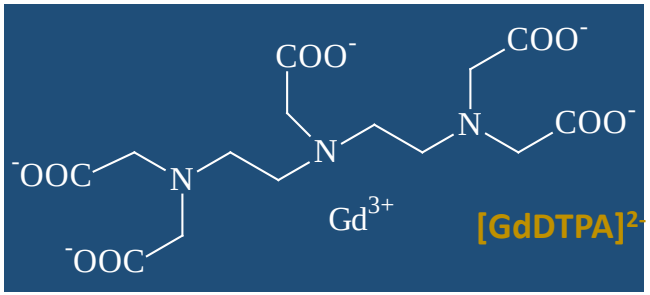
A MR-image represents a map of the intensity of

the ^{1}H-NMR signal of water protons

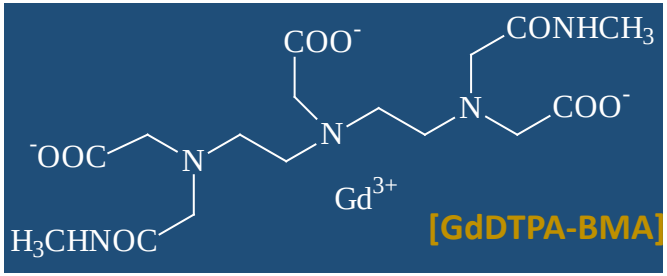
The contrast is mainly generated by difference

in the relaxation times (T_1 and T_2) of water protons

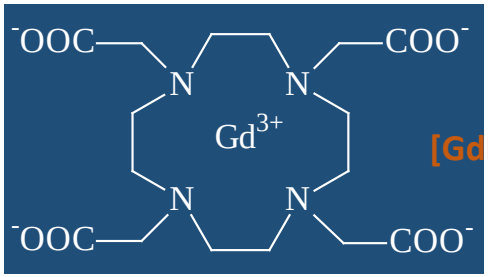
Extracellular Gd(III)-based agents in the clinical practice



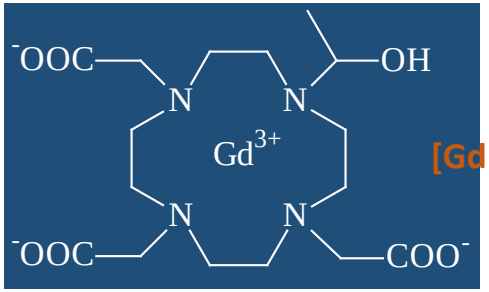
[GdDTPA]$^{2-}$ (Magnevist®)



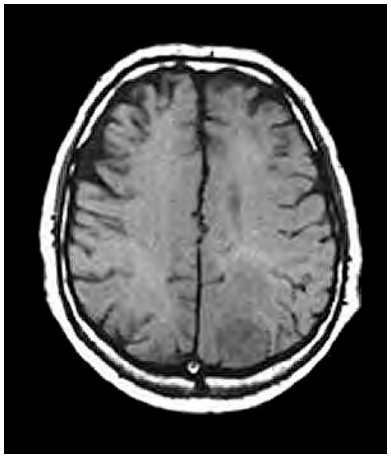
[GdDTPA-BMA] (Omniscan®)



[GdDOTA]$^{-}$ (Dotarem®)



[GdHPDO3A] (ProHance®)



Without CA

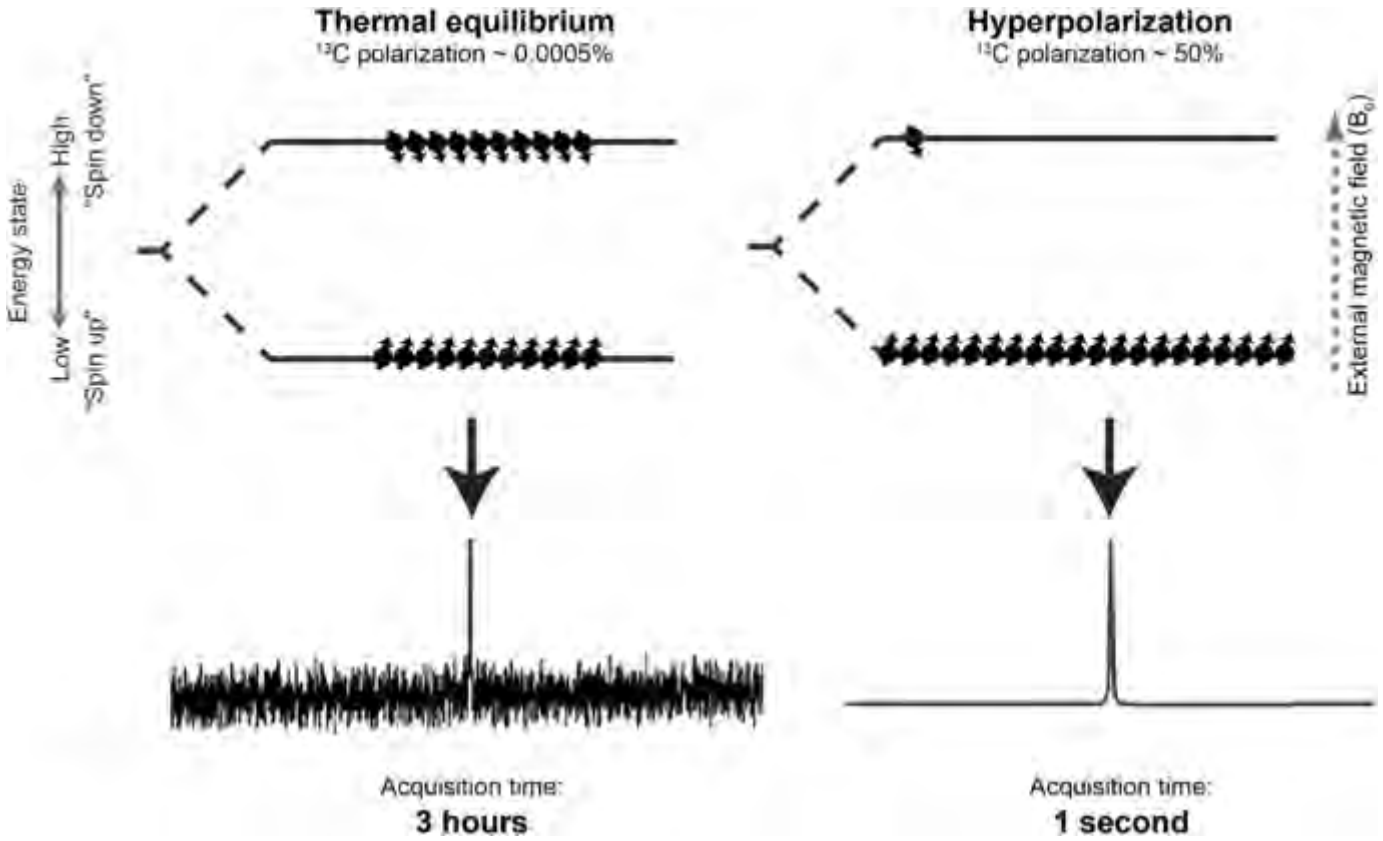
With Gd(III)-based CA

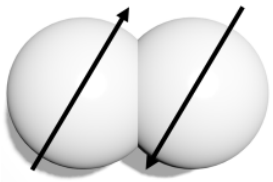
La Risonanza Magnetica, mentre possiede una superba risoluzione spaziale, ha un limite di sensibilità rispetto alle altre tecniche

Principali soluzioni adottate per superare il problema della bassa sensibilità del MRI per applicazioni di Molecular Imaging:

- **Accumulare grandi quantità di agente di contrasto** al target sfruttando trasportatori di membrana ad alta capacità.
- **Progettare nuovi sistemi che sfruttino un effetto di amplificazione** per esempio basato sullo scambio di protoni con l'acqua.
- **Acquisire immagini di nuclei diversi da H-1** per eliminare il background, es. F-19.
- **Applicare metodi di Iperpolarizzazione**

Hyperpolarization: the route to solve the sensitivity issue





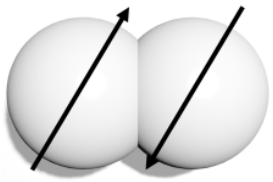
Parahydrogen Induced Polarization (PHIP)

SEOP
Spin Exchange Optical Pumping of noble gases

Hyperpolarization

dissolution-Dynamic Nuclear Polarization (d-DNP)

Brute force



Parahydrogen Induced Polarization (PHIP)

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Dynamic Nuclear Polarization

T~1K

+

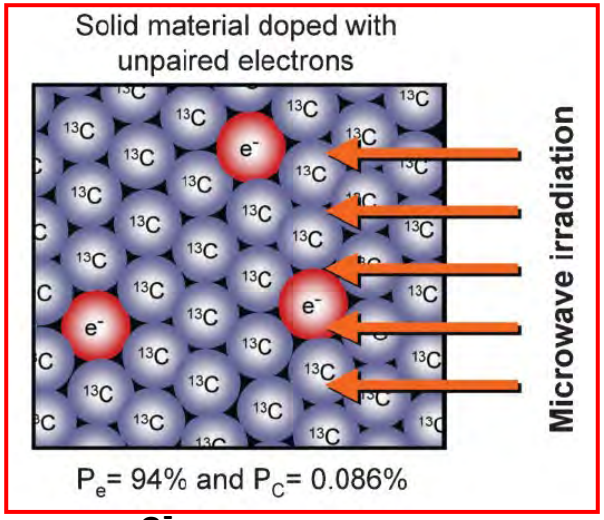
$$P = \tanh\left(\frac{\gamma \hbar B_0}{2k_B T}\right)$$

B_0= 3.35T, T=1.2K

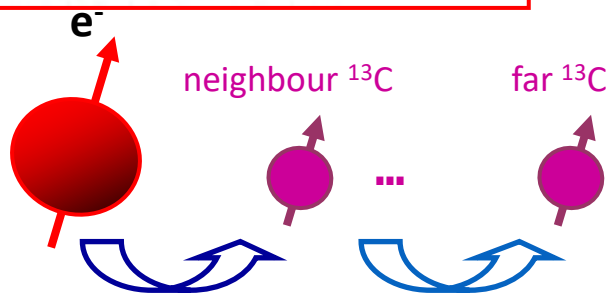
e^- → P=0.95

^{13}C → $P=7\cdot10^{-4}$

(g_{el}~2600 γ_{13C})



Through MW polarization is transferred from electron to nuclei.



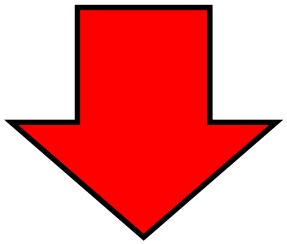
Overhauser (through MW)

Hyperfine interaction between nuclei and electrons

Spin diffusion

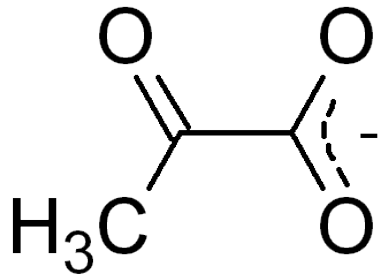
Dipolar interaction between nuclei

MRI with Hyperpolarized Probes



Metabolic Imaging

Hyperpolarization



Pyruvate

Transamination

Oxidative Decarboxylation

Reduction

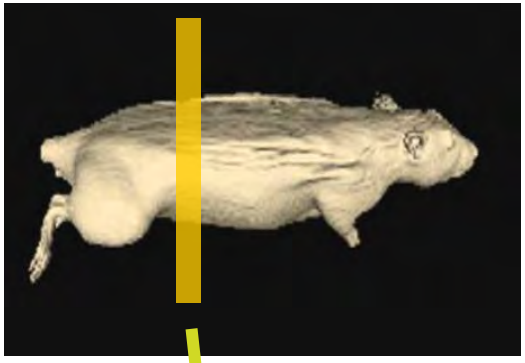
Alanine

CO_2

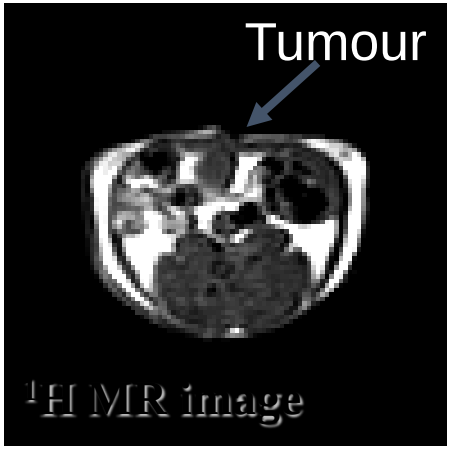
Lactate

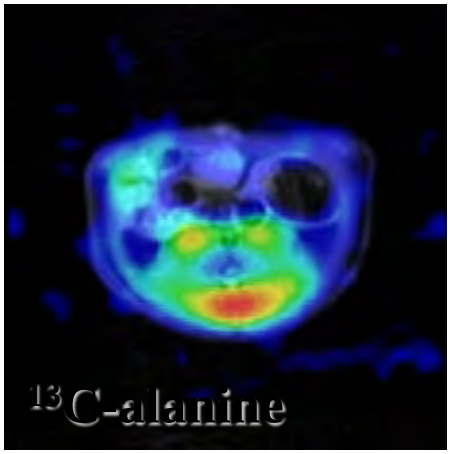
Acetyl-CoA

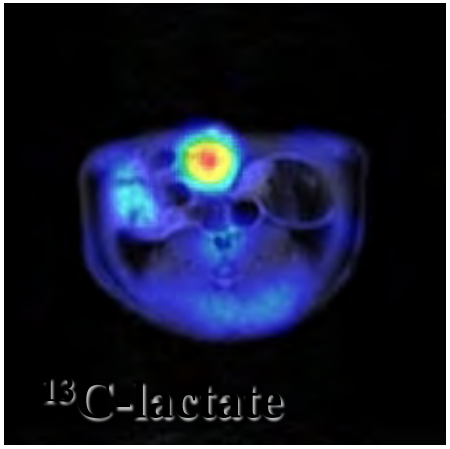
Metabolic contrast after injection of ^{13}C-pyruvate (20% polarized) in rat bearing a P22 tumour



Metabolic ^{13}C images (0.2 cc voxels) obtained on 1.5 T Sonata in 15 seconds !!



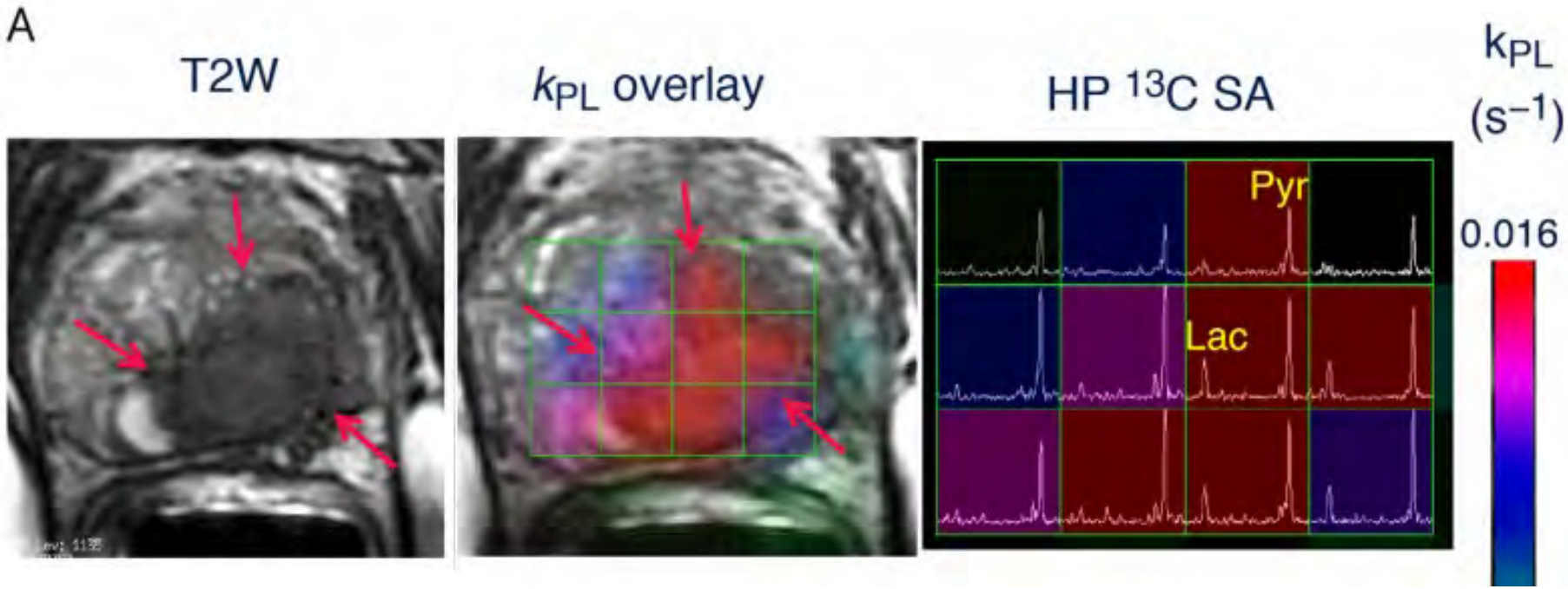




Courtesy: R. in ‘t Zandt, Amersham, Malmo, SE

imagination at work

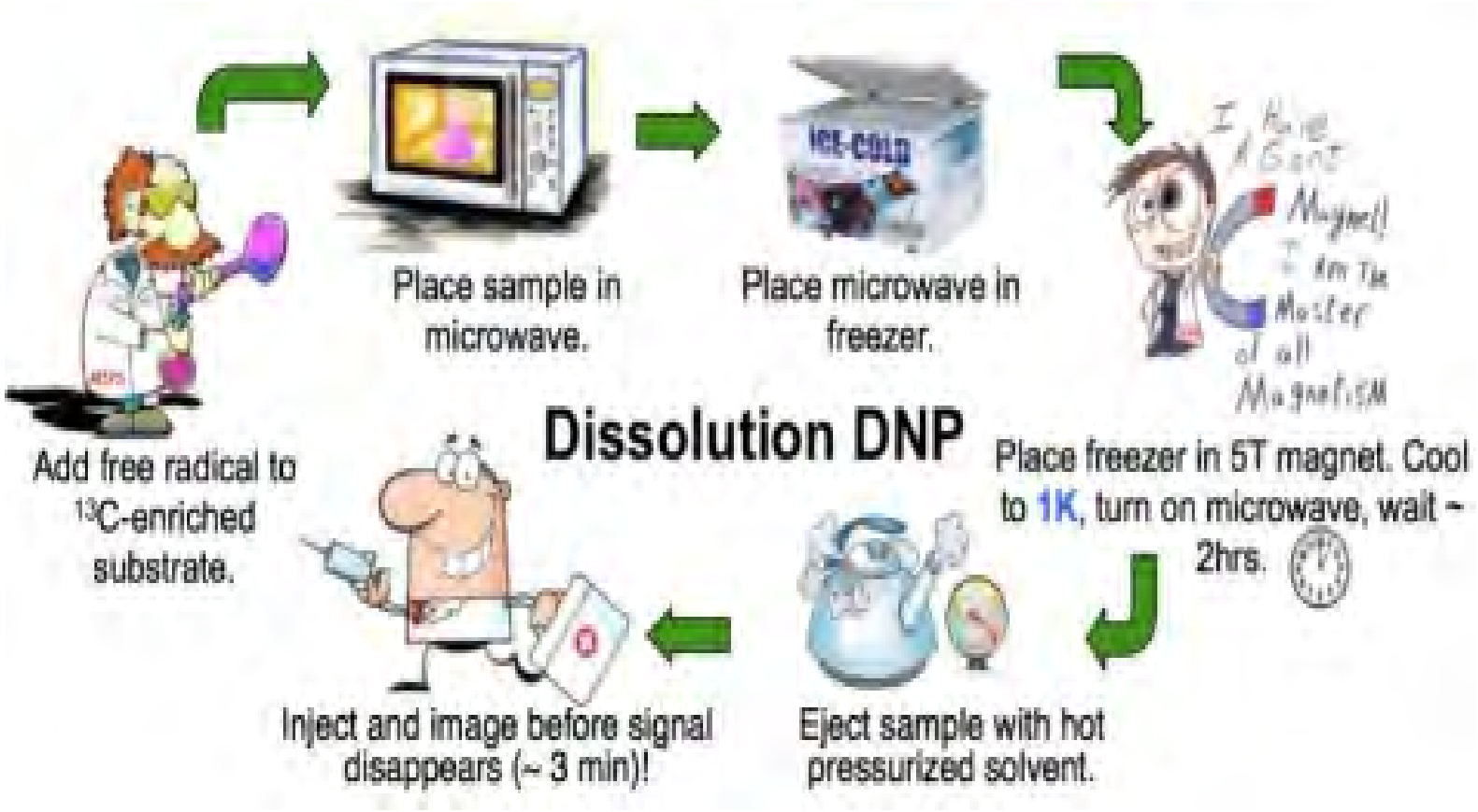
Human application: Pyruvate as reporter of aggressiveness in prostate cancer

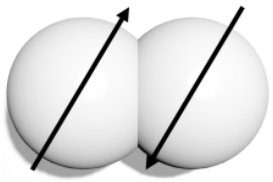


Representative axial T2-weighted (T2W) anatomic image and T2W image with an overlaid pyruvate-to-lactate metabolic flux (k_{PL}) image and corresponding hyperpolarized (HP) ^{13}C spectral array (SA) for a 52-yr-old prostate cancer patient with extensive high-grade prostate cancer

Aggarwal, 2017

Dynamic Nuclear Polarization (DNP) is a high technologically demanding and expensive procedure





Parahydrogen Induced Polarization (PHIP)

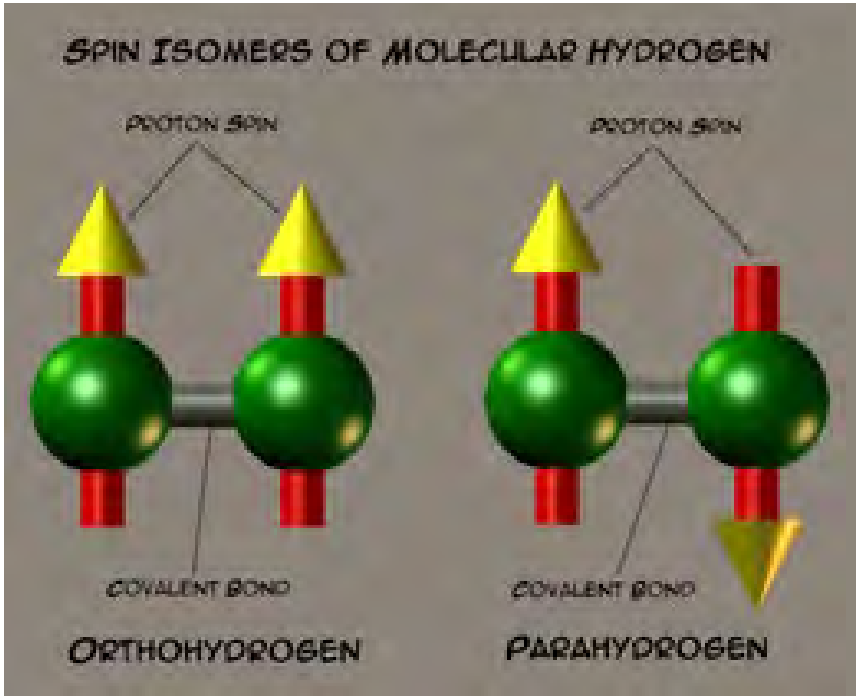
SEOP
Spin Exchange Optical Pumping of noble gases

Hyperpolarization

dissolution-Dynamic Nuclear Polarization (d-DNP)

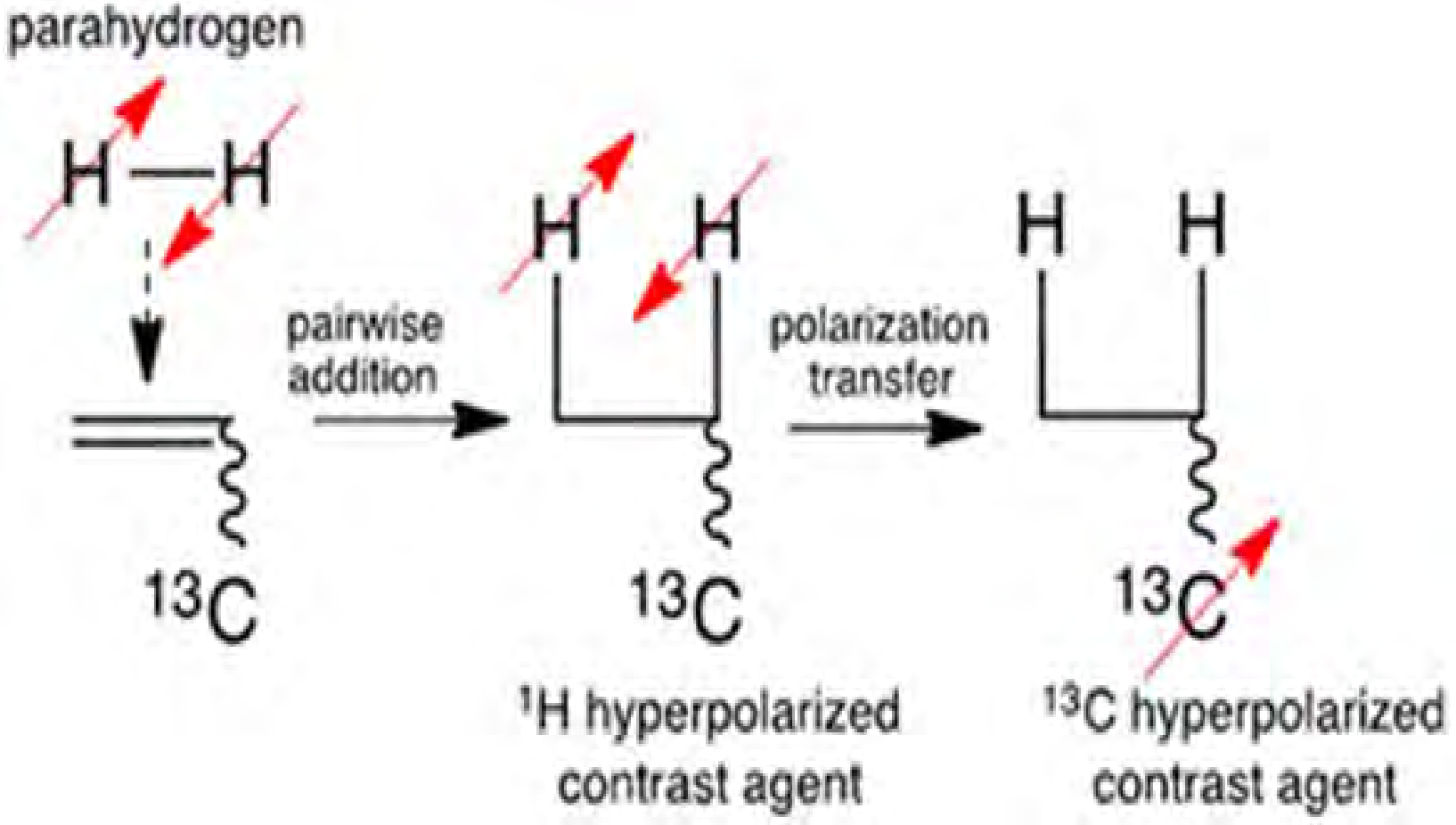
Brute force

Molecular hydrogen occurs in two isomeric forms, one with its two proton nuclear spins aligned parallel (orthohydrogen), the other with its two proton spins aligned antiparallel (parahydrogen)

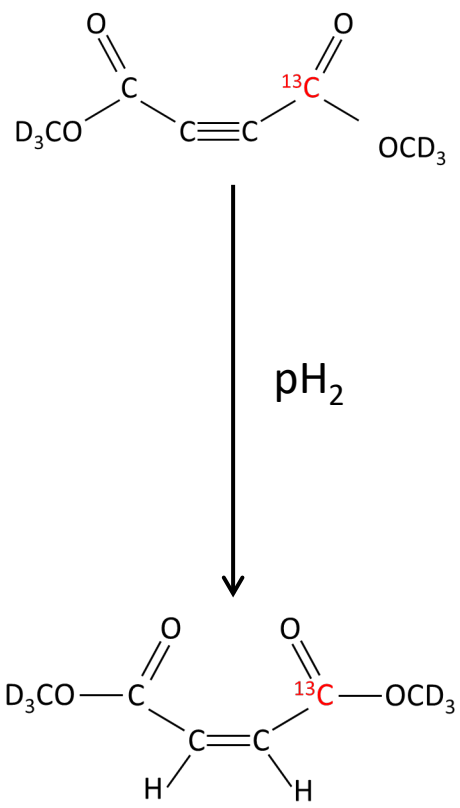


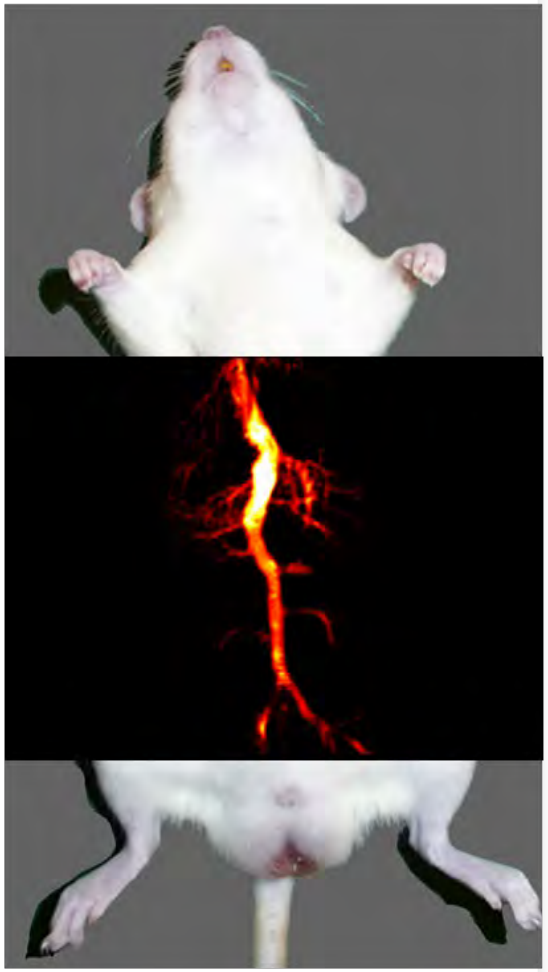
Parahydrogen is in a lower energy state than is orthohydrogen. At room temperature approximately 75% orthohydrogen and 25% parahydrogen. Enrichment in the parahydrogen form can be obtained at very low temperatures, in the presence of a catalyst (iron oxide, charcoal,..).

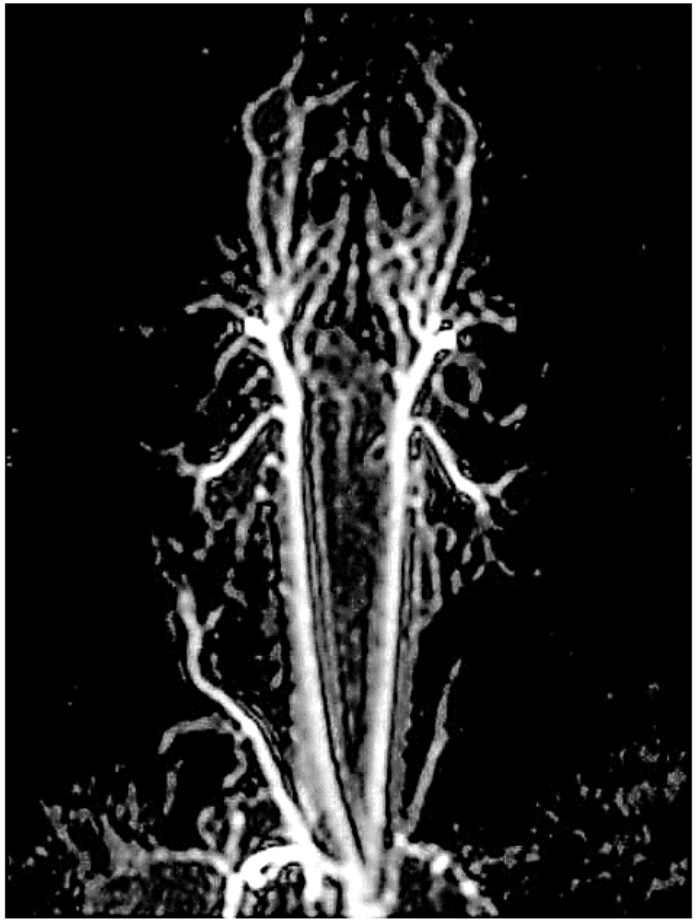
Para-Hydrogen Induced Polarization (PHIP)



PHIP application: angiography with C-13 detection



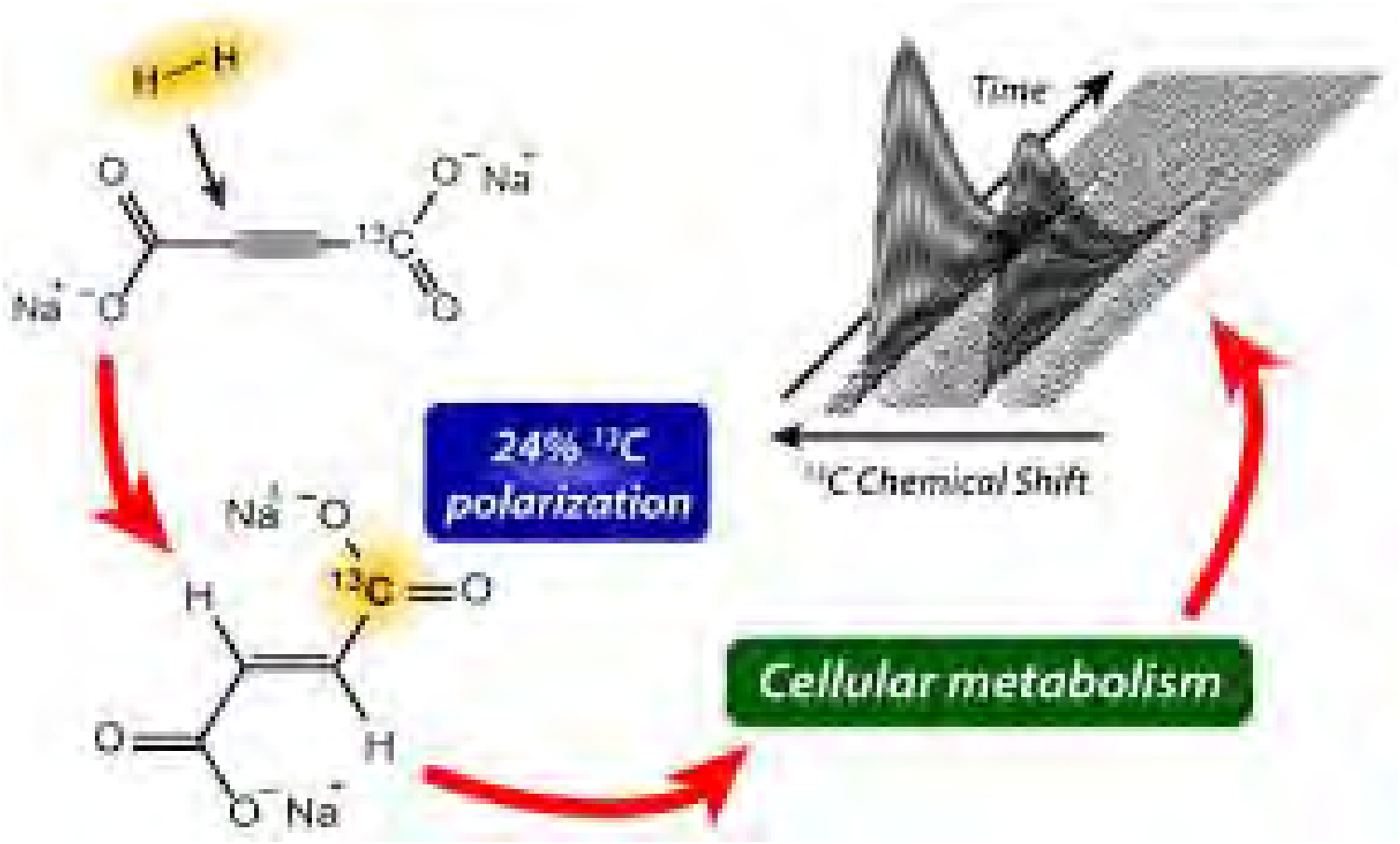




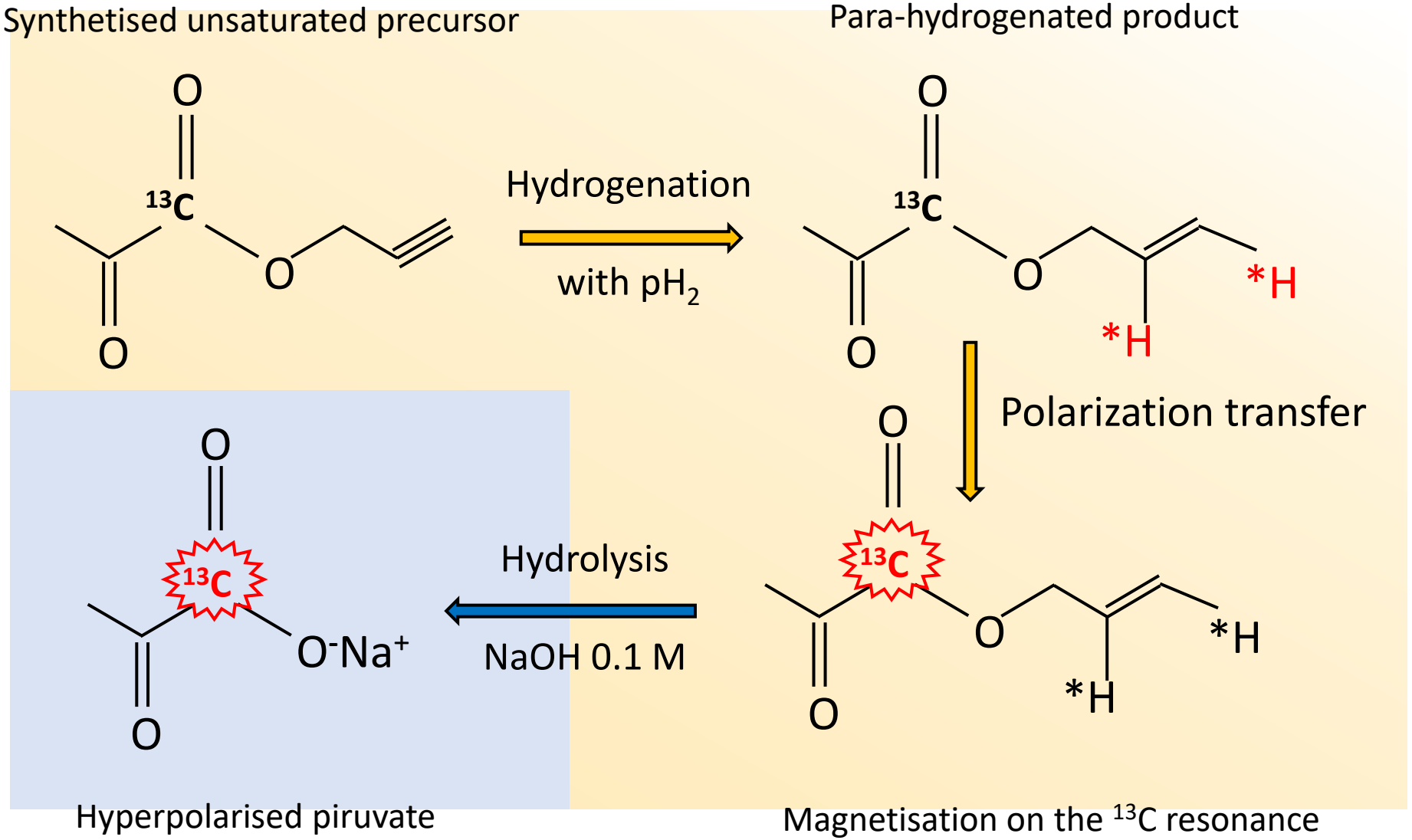
Angiogram depicting the arteries in a guinea pig head.
S. Måansson, et al; Eur Radiol **16**: 57-67 (2016)

Real-Time Nuclear Magnetic Resonance Detection of Fumarase Activity Using Parahydrogen-Hyperpolarized [1-13C]Fumarate.

Journal of the American Chemical Society, DOI: 10.1021/jacs.9b10094



PHIP-Side Arm Hydrogenation (PHIP-SAH): the route to Hyperpolarize substrates for which de-hydrogenated precursors are non naturally available



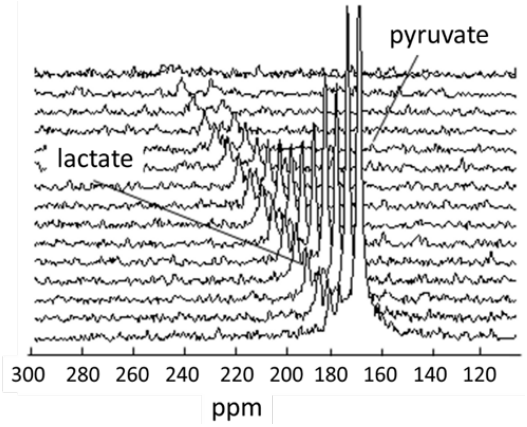
PHIP-SAH [1-^{13}C]pyruvate: *in vivo* heart metabolism at 1T

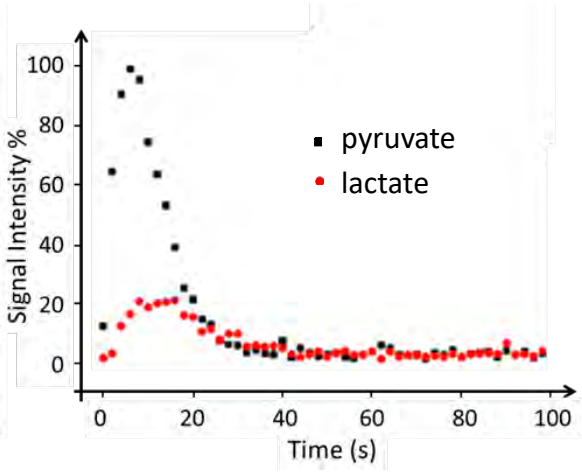
Spatially localized ^{13}C-MRS slice centred on the heart of a 6 months mice

Lmna$^{H222P/H222P}$ mice striated muscle-specific laminopathies [1]:

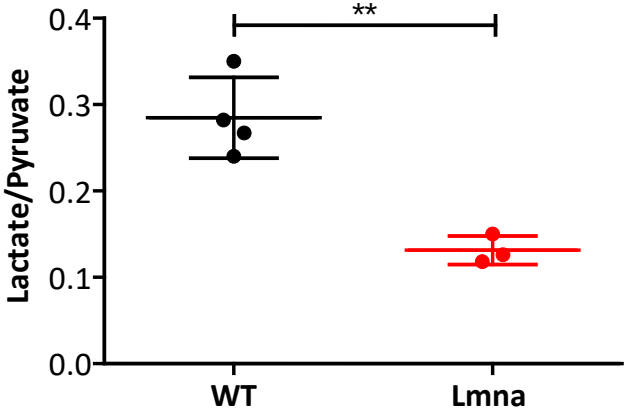
. muscular dystrophy

. heart failure





Model free approach analysis
AUC (Area Under the Curve)
Lactate/Pyruvate



PHIP-SAH technology

pH_2 generators

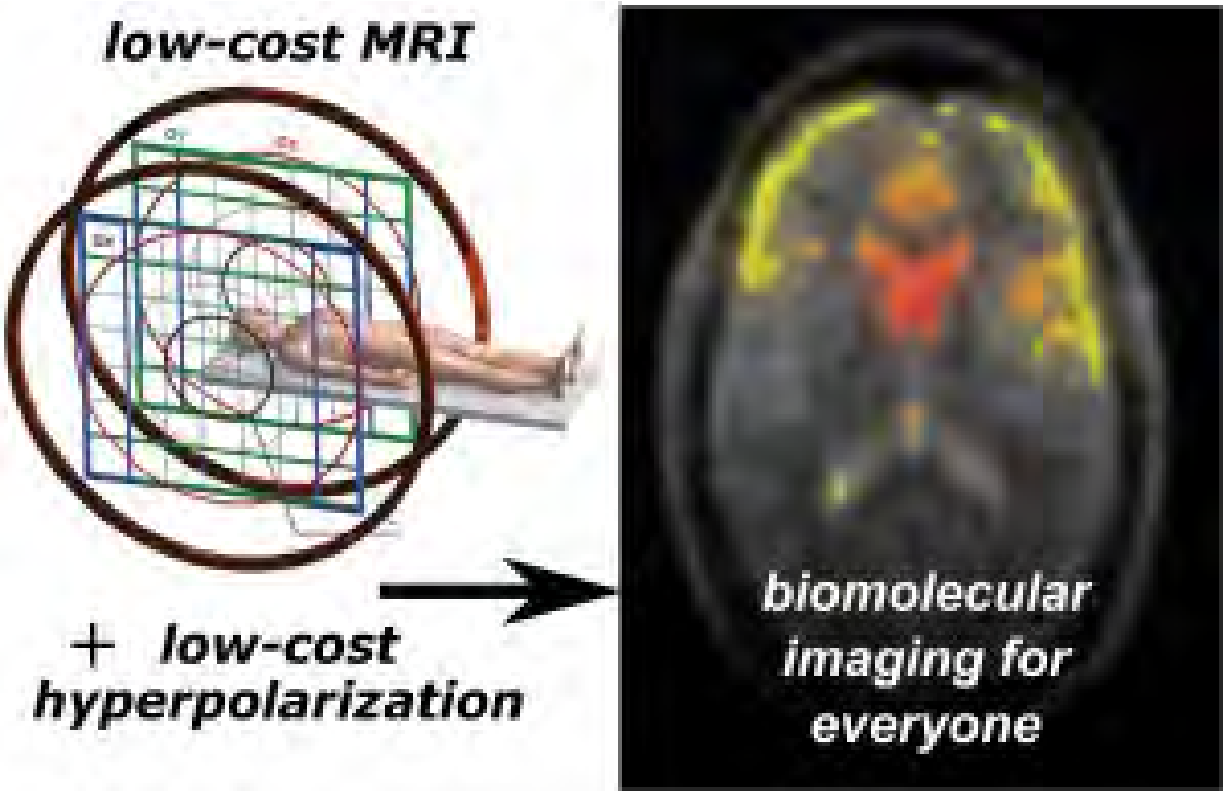
paraHydrogenation

Polarizer

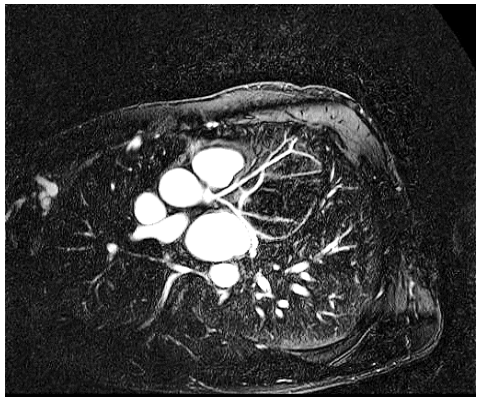
Hydroysis

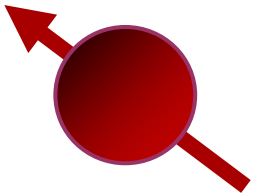
Quality Control
pH, Pol %, impurities

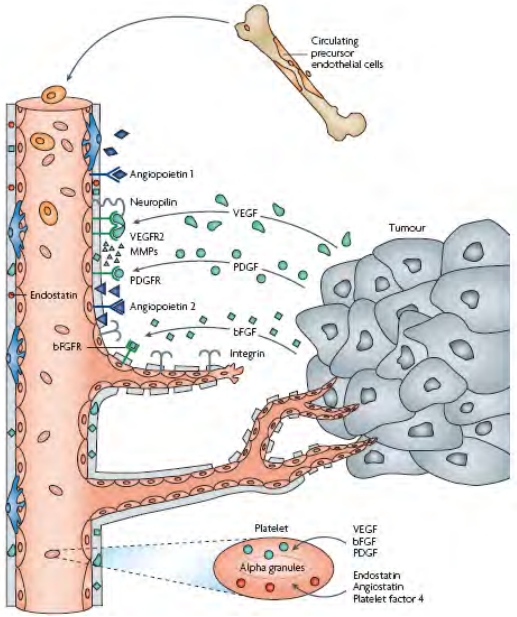
Affordable Molecular Imaging by Hyperpolarized Low-Field MRI



From …







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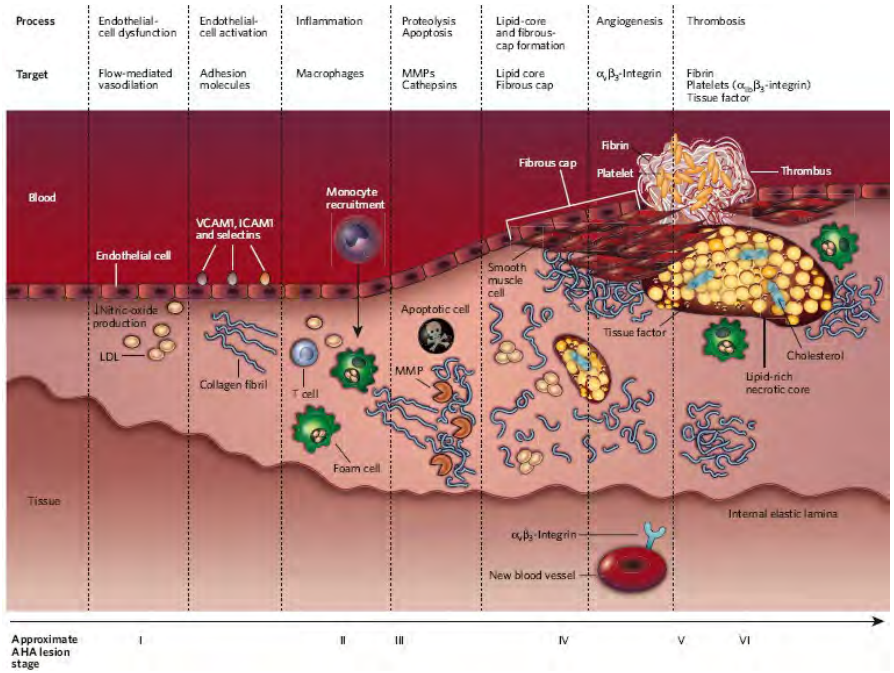

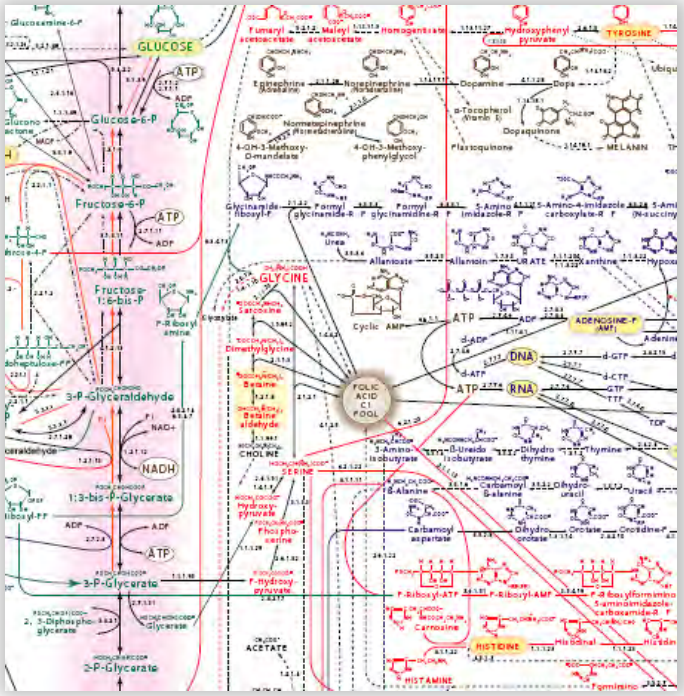

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THANK
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