Is There Still Innovation in Contrast Media ?

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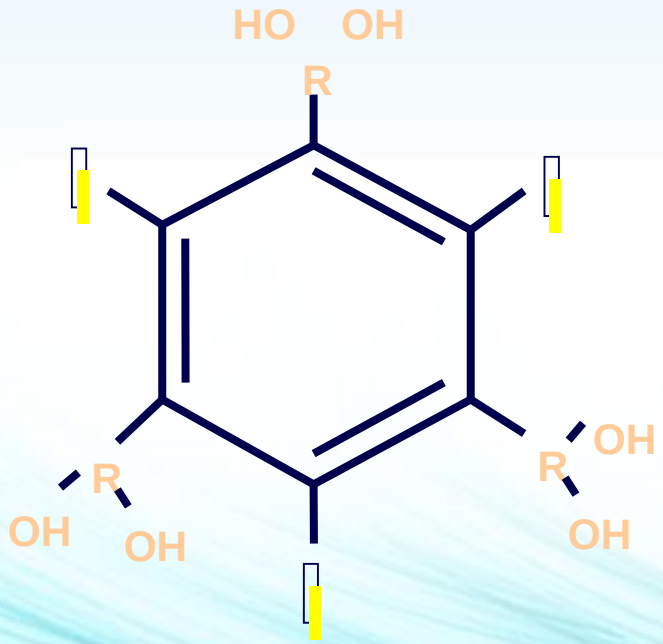
HISTORY

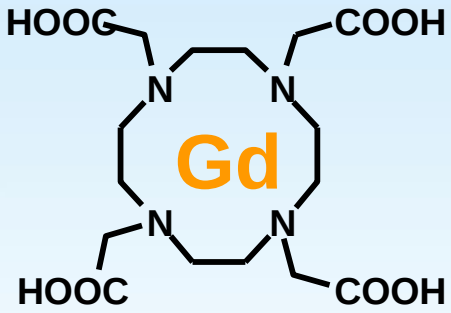
- Innovation in Contrast Media has been very active in the last 50 years
  - 70 – 80s : Non Ionic Iodinated agents



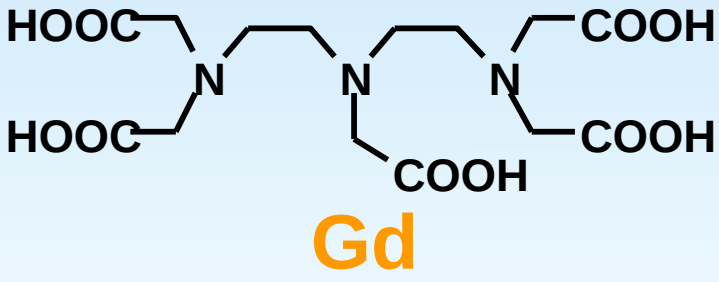
- **Iobitridol Xenetix**
- **Iohexol Omnipaque**
- **Iopentol Ivepaque**
- **Iopamidol Iopamiron**
- **Iopromide Ultravist**
- **Ioversol Optiray**
- **Iomeprol Iomeron**

HISTORY

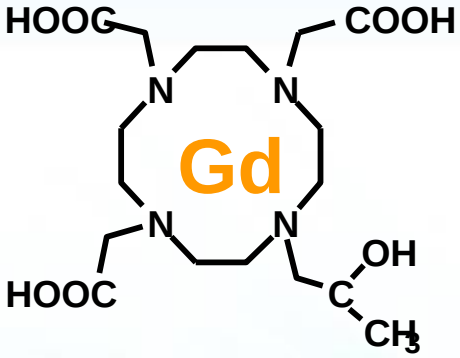
- 90s MRI Gadolinium chelates



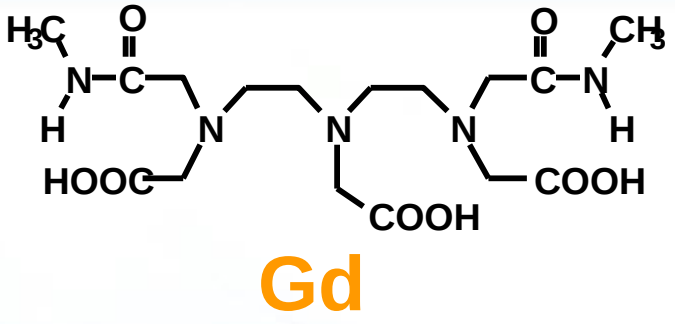
DOTA (Dotarem®)



DTPA (Magnevist®)



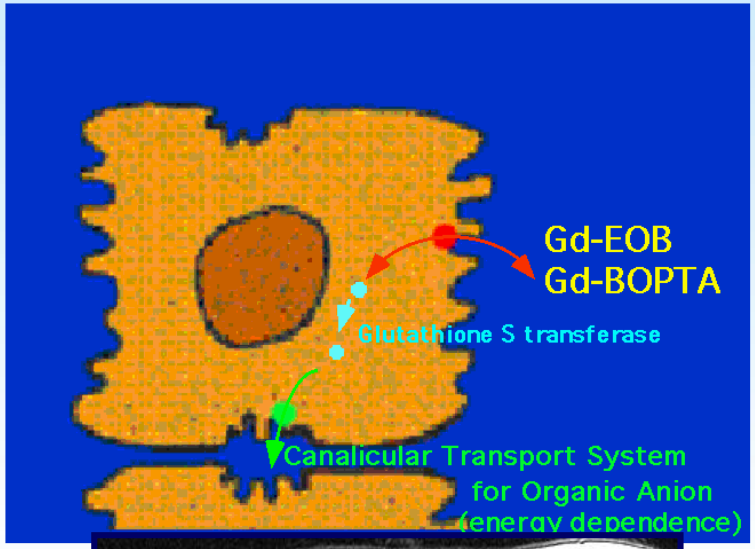
HP-DO3A (ProHance®)

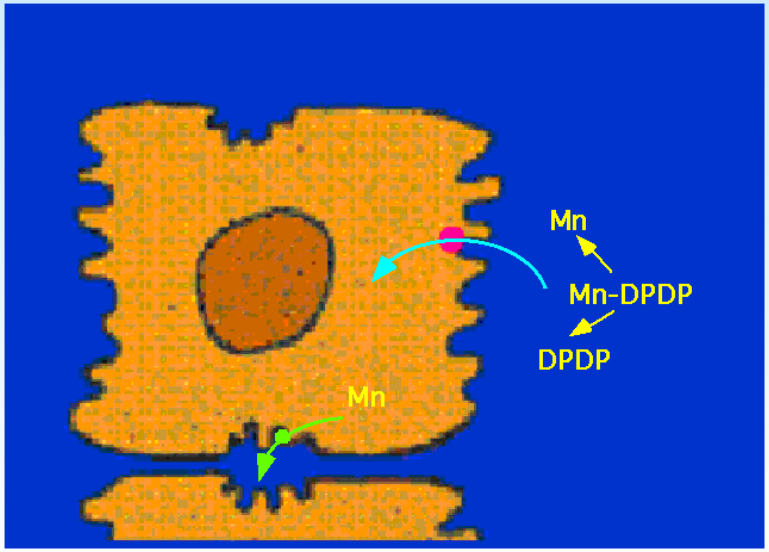


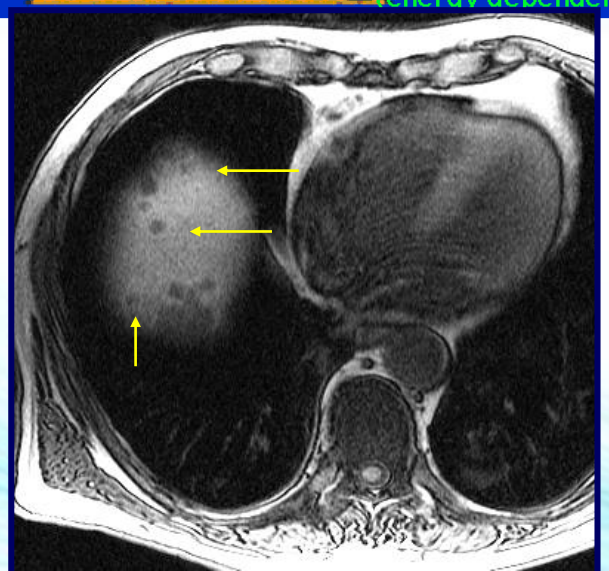
DTPA-BMA (Omniscan®)

HISTORY

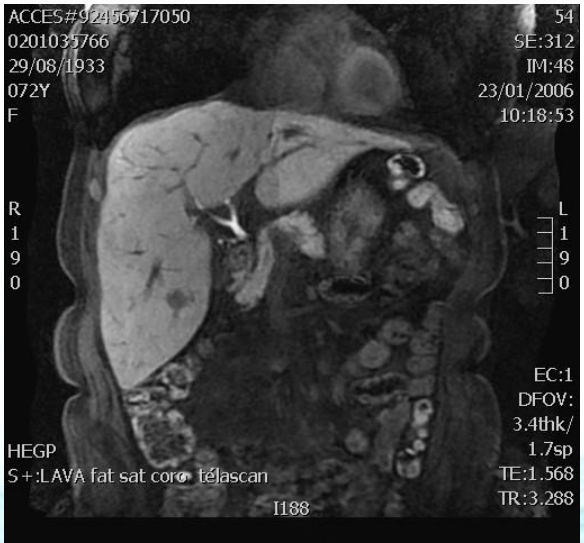
- 90s MRI agents Liver specific agents







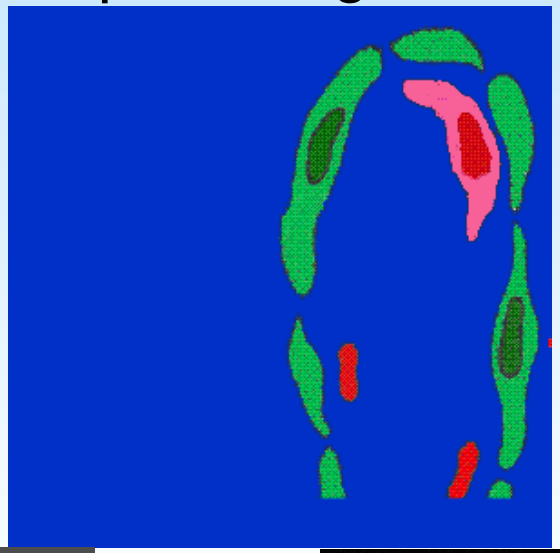
Primovist

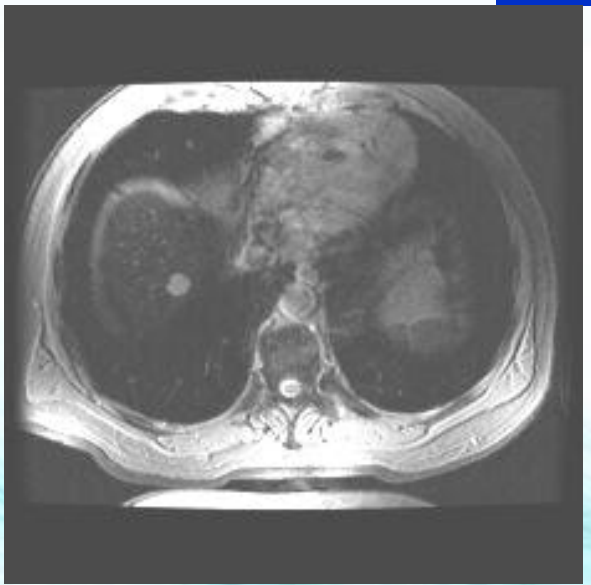


Teslascan

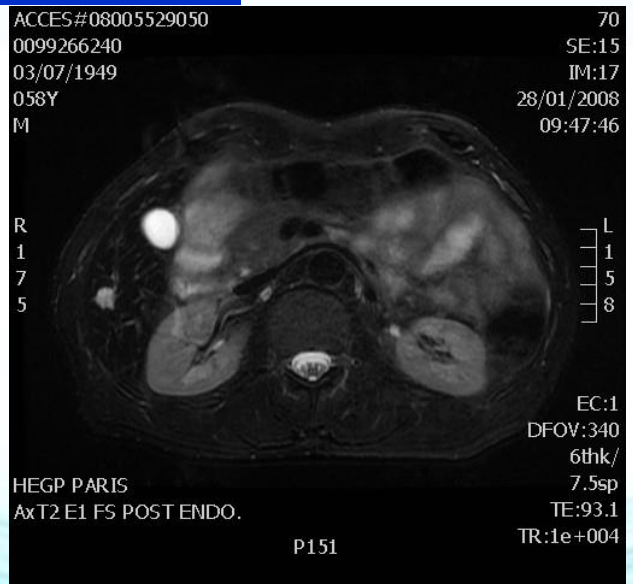
HISTORY

- 90s MRI agents Liver specific agents





Endorem

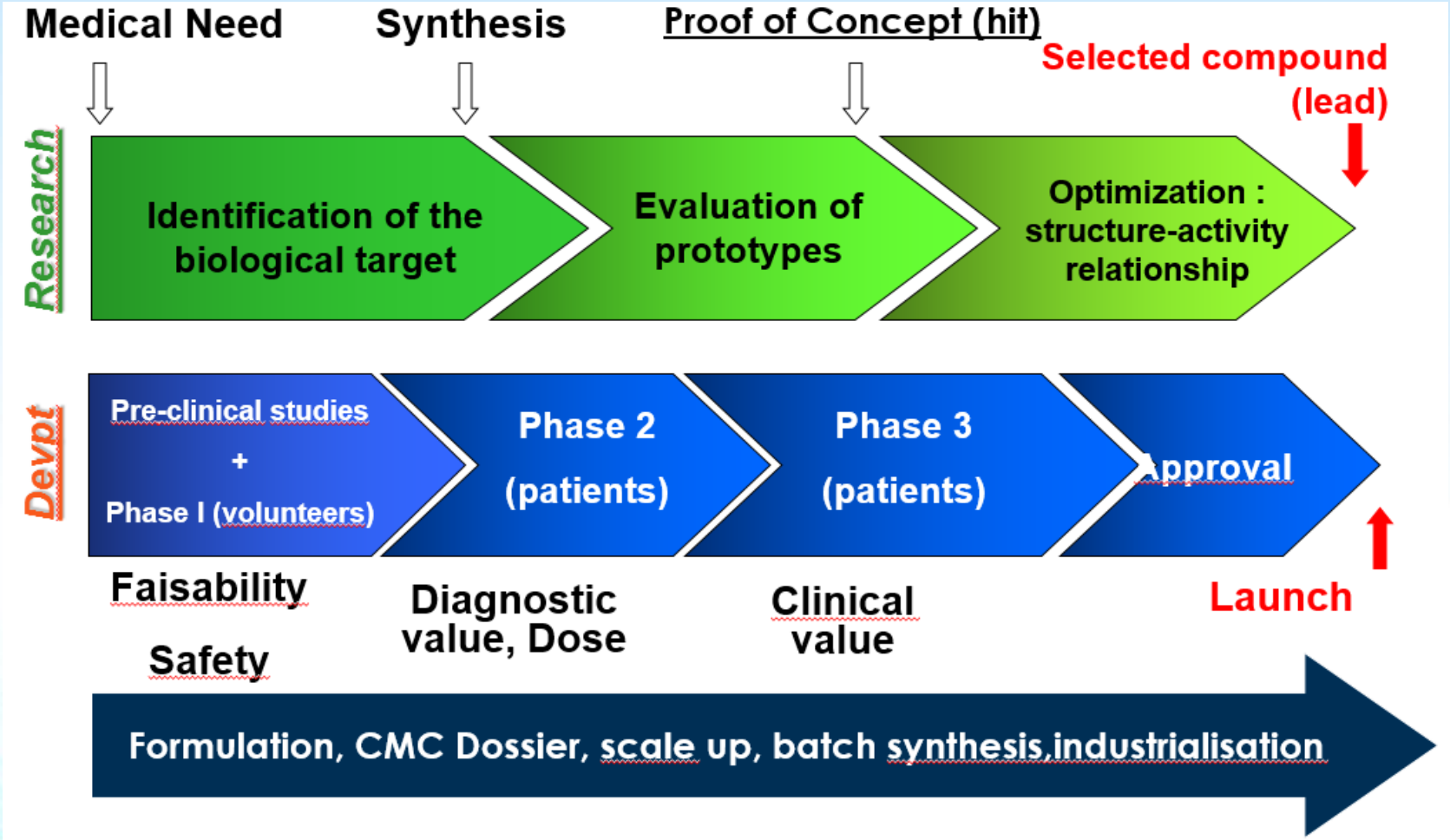


Resovist

HISTORY

- Innovation in Contrast Media has been very active in the last 50 years
  - 90s Ultrasound agents Macromolecular agents
  - 2000 Molecular Imaging

Contrast Media are Pharmaceutical Compounds → Drugs Regulatory Legislation



From the Medical Need to the Drug

10 years !!

What do we get ?

Registered products

Non specific Gd Chelates

Macrocyclic

Dotarem
Prohance
Gadovist

Linear

Magnevist
Omniscan
Optimark
Multihance

Authorities warning or withdrawal (EU)

Blood Pool Agent

Ablavar : withdrawn

Liver Imaging

Marketed

Eovist/
Primovist
Multihance

Withdrawn

Mn : Teslascan
SPIO :
Endorem/Ferridex
Resovist (except JPN)

Iron Deficiency

Feraheme USPIO
Imaging off label use

Oral use Withdrawn

Abdoscan MPIO
Lumirem MPIO

Development

Non Specific Gd Chelates

Gadopiclenol

Thrombosis

EP2114
Phase 2a Stop

Blood Pool Agent

Vistarem Phase 2 stop
Gadomer Phase 1 stop

Angiogenesis

Kereos 19F-NP
Phase 1 Stop

USPIO

Sinerem/Combidex Phase 3 stop
Clariscan : Phase 2a stop
Supravist : Phase 2a stop
VSOP Phase 2a stop
P904 : IMPD stop

Contrast Media Research Meetings

- Initiated in 1970, focused on tolerance, then new agents
- Informal structure every 2 years

CMR Meeting 2017: sessions

	SAFETY	NEW AGENTS	NEW APPLICATIONS
IODINATED AGENTS	1	2	
MR CA	3	4	2
Molecular Imaging		2	
Ultrasound CA		1	1
Optical CA		2	

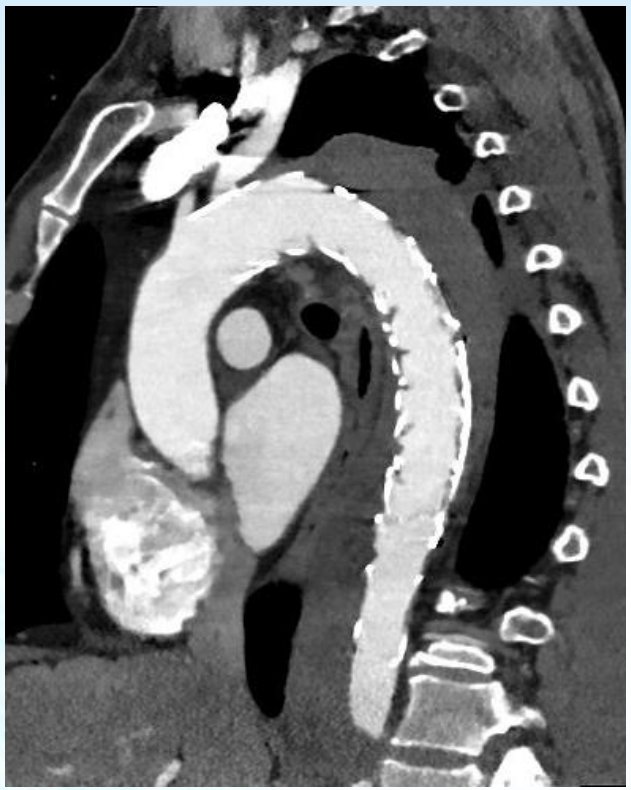
http://contrastmediaresearch.org/wp-content/uploads/2017/10/CMR-Full-Agenda-FINAL-LW-v8.pdf

TENDENCIES IN CM Research

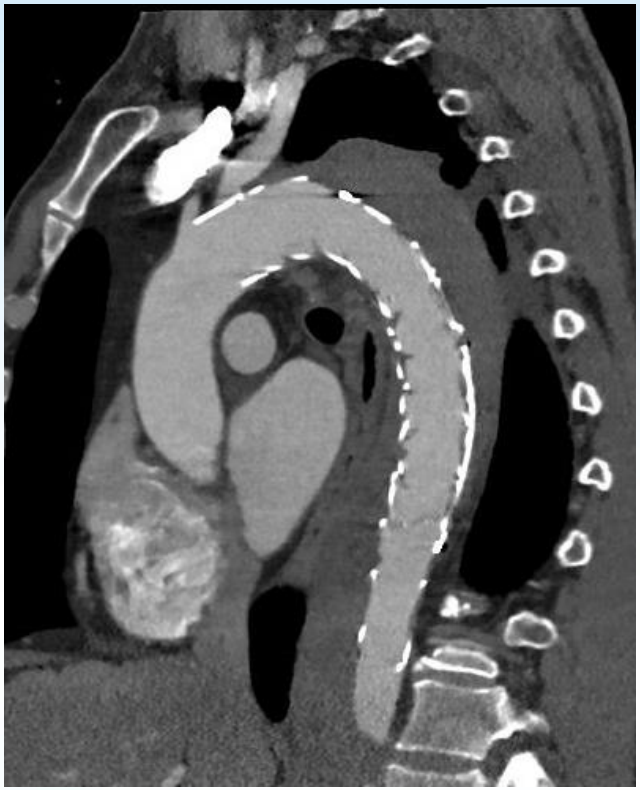
- X-ray
  - new CA for multi-energy CT imaging
- MRI
  - Non Gd agents
  - Gd-based new Agents (high-relaxivity, macrocyclic)
- Ultrasound (US)
  - Mol imaging
- Optical: surgery and endoscopy

Double energy

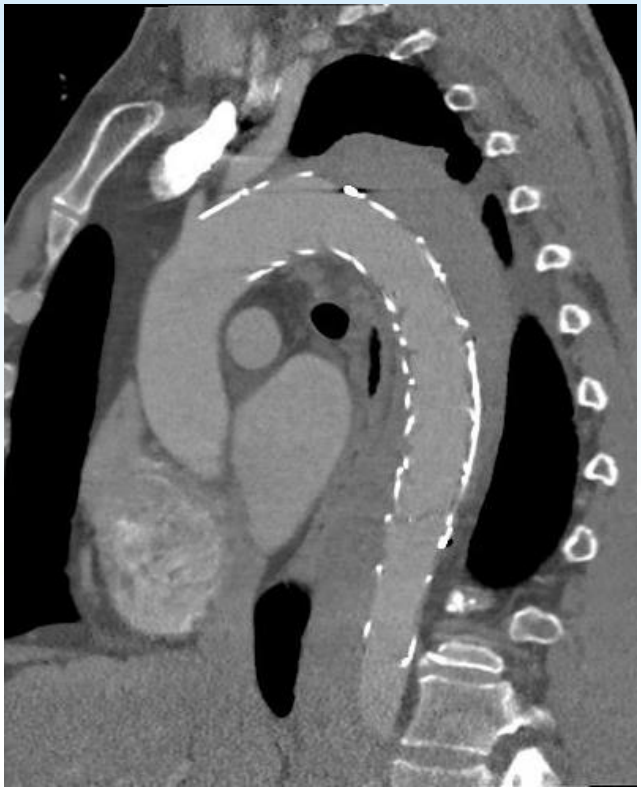
Monoenergy reconstruction



54 keV



70 keV



120 keV

IODINE MAPS

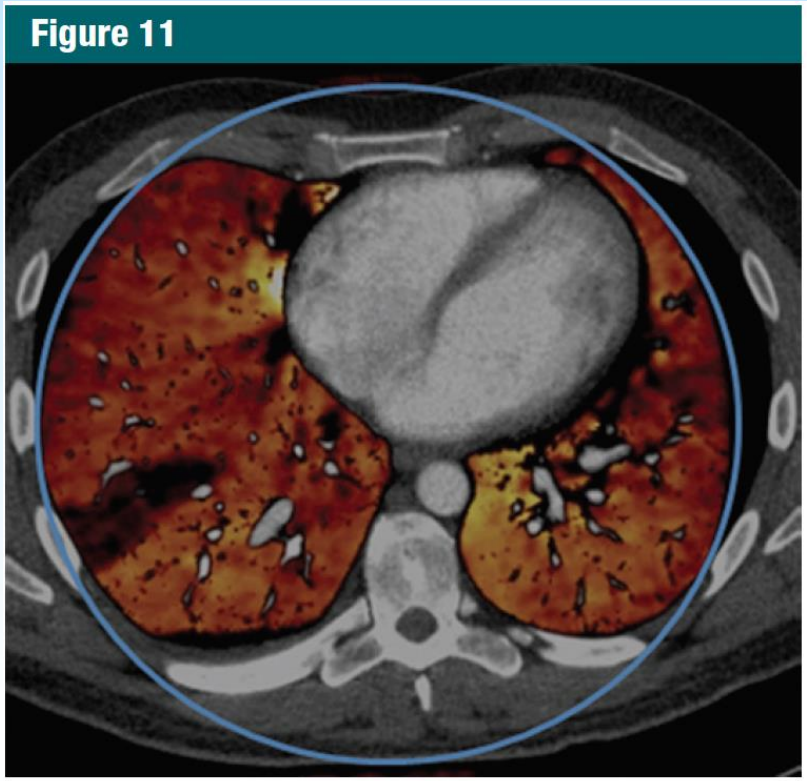


Figure 11: Contrast-enhanced, dual-energy axial CT image in a 31-year-old man with a pulmonary embolism in the right lower lobe. Iodine signal is identified and color coded in red within the segmented lung. The iodine overlay image is superimposed on a gray-scale mixed image. The dark regions show a perfusion defect secondary to the embolism. Blue circle marks the diameter of the second tube on the dual-source CT scanner. Dual-energy data are acquired only within this circle.

McCollough, Radiology 2015

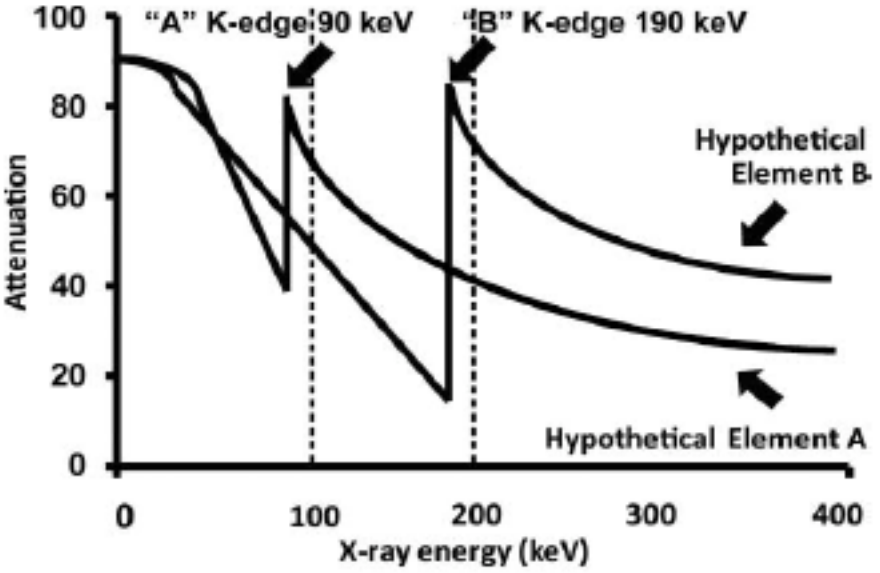
- Better visualisation of Iodine
- Lowering the dose and concentrations

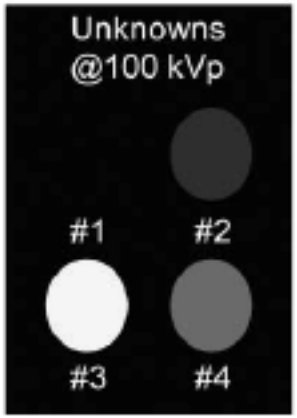
DIFFERENTIATION OF MATERIALS

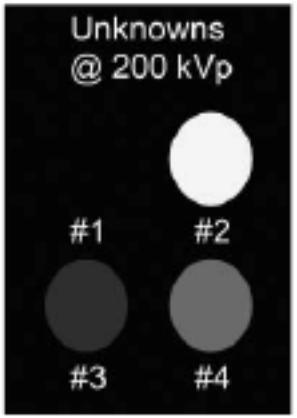
$$\mu = \rho[\sigma_\tau + \sigma_R + \sigma_C]$$

K Edges and Atomic Numbers of Physiologic Substances and Contrast Agents

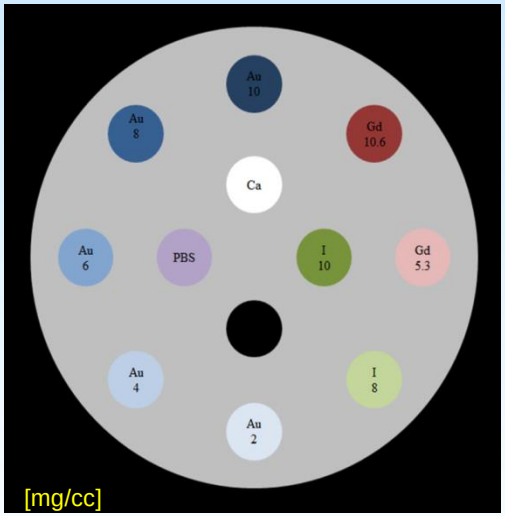
Substance	K Edge (keV)	Atomic Number (Z)
Hydrogen	0.01	1
Carbon	0.28	6
Nitrogen	0.40	7
Oxygen	0.53	8
Calcium	4.00	20
Iodine	33.20	53
Barium	37.45	56
Gadolinium	50.20	64

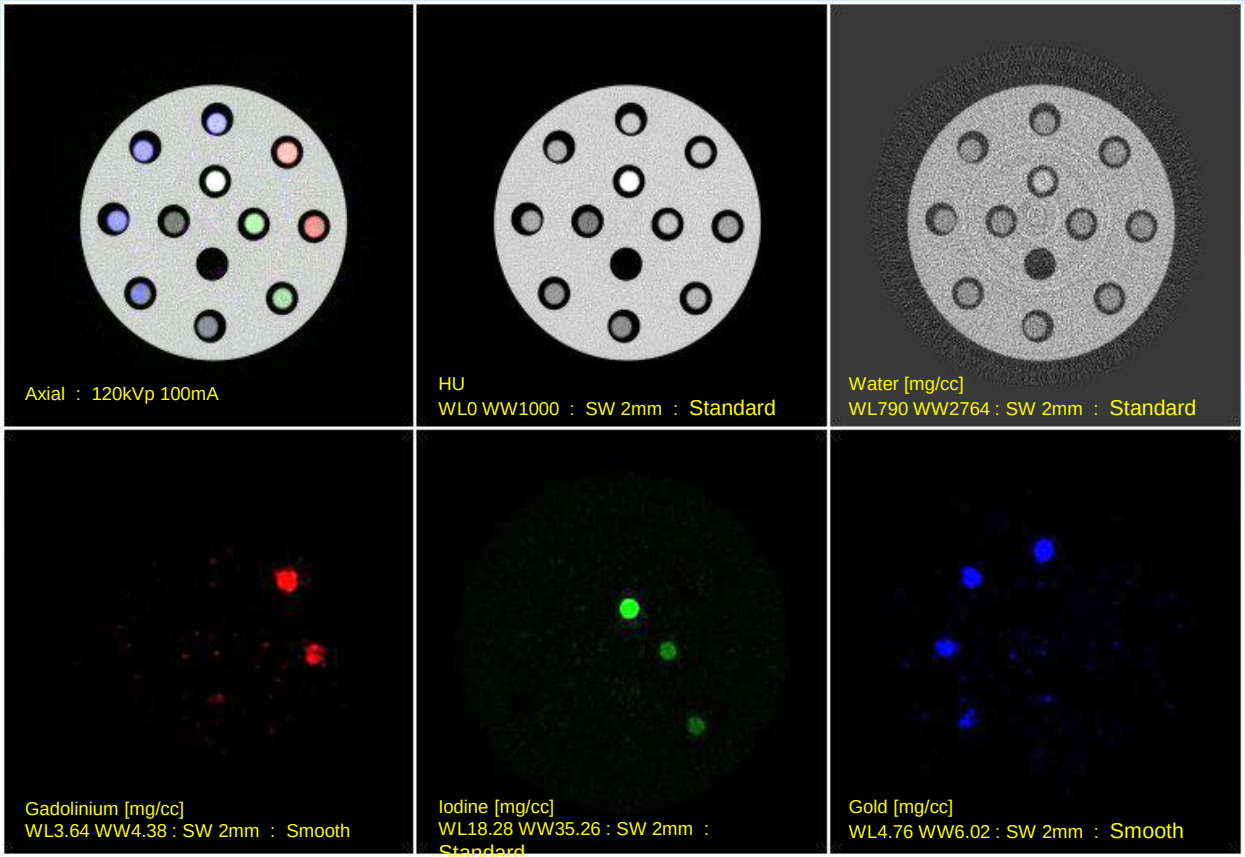






DECOMPOSITION K EDGE





New CM : Au, Bi, Ta ?

Penn
University of Pennsylvania

Lyon university partnership with: University of Pennsylvania

Tantalum Nanoparticles

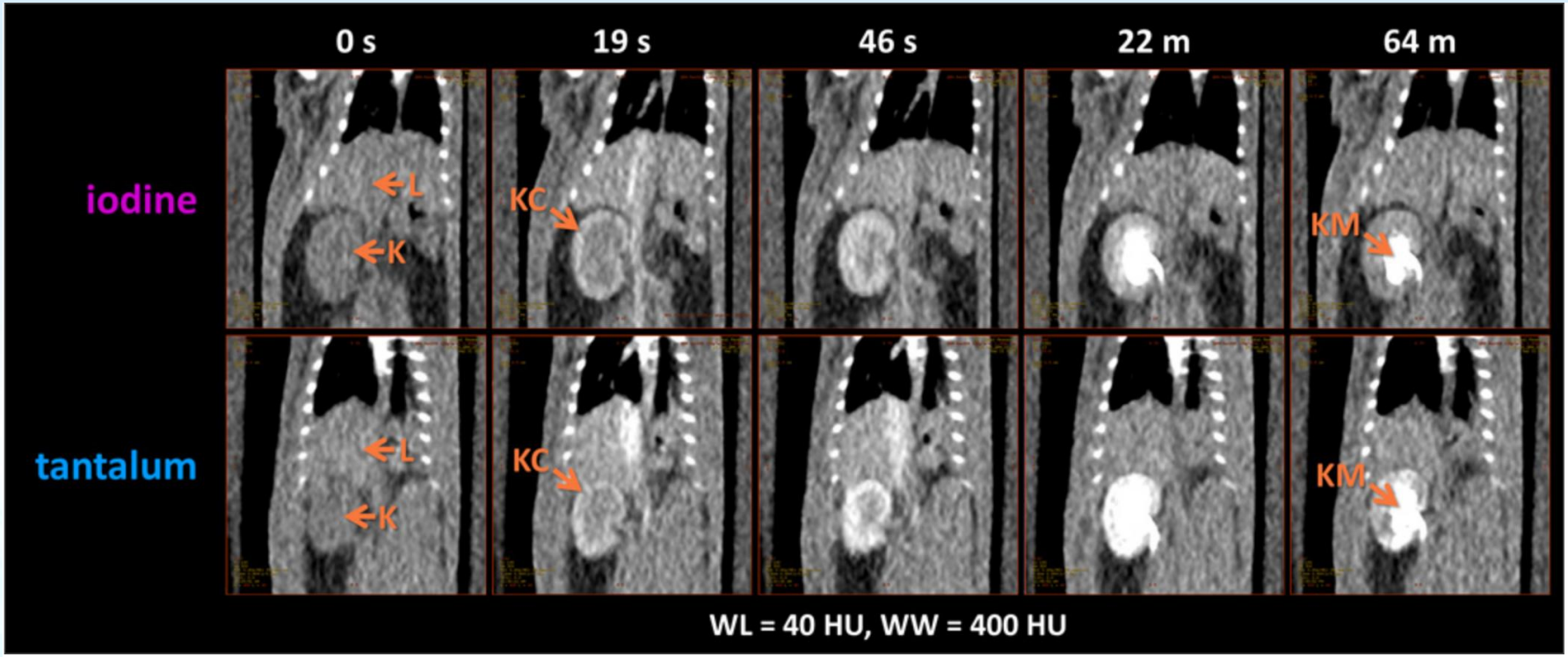


Figure 6

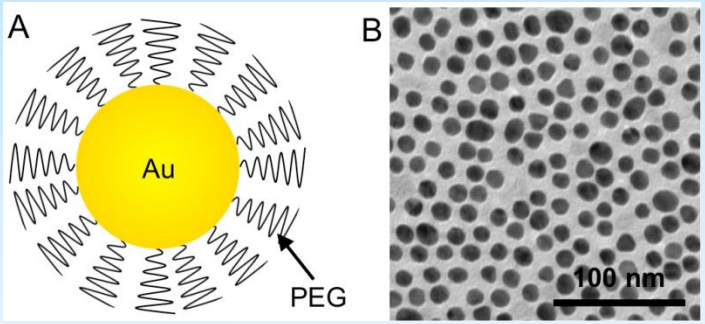
Typical CT images showing liver and kidney enhancement in normal rats, using iodine (iopromide) and tantalum (CZ-TaO NPs). Key: L=liver; K=kidney; KC=kidney cortex; KM= kidney medulla.

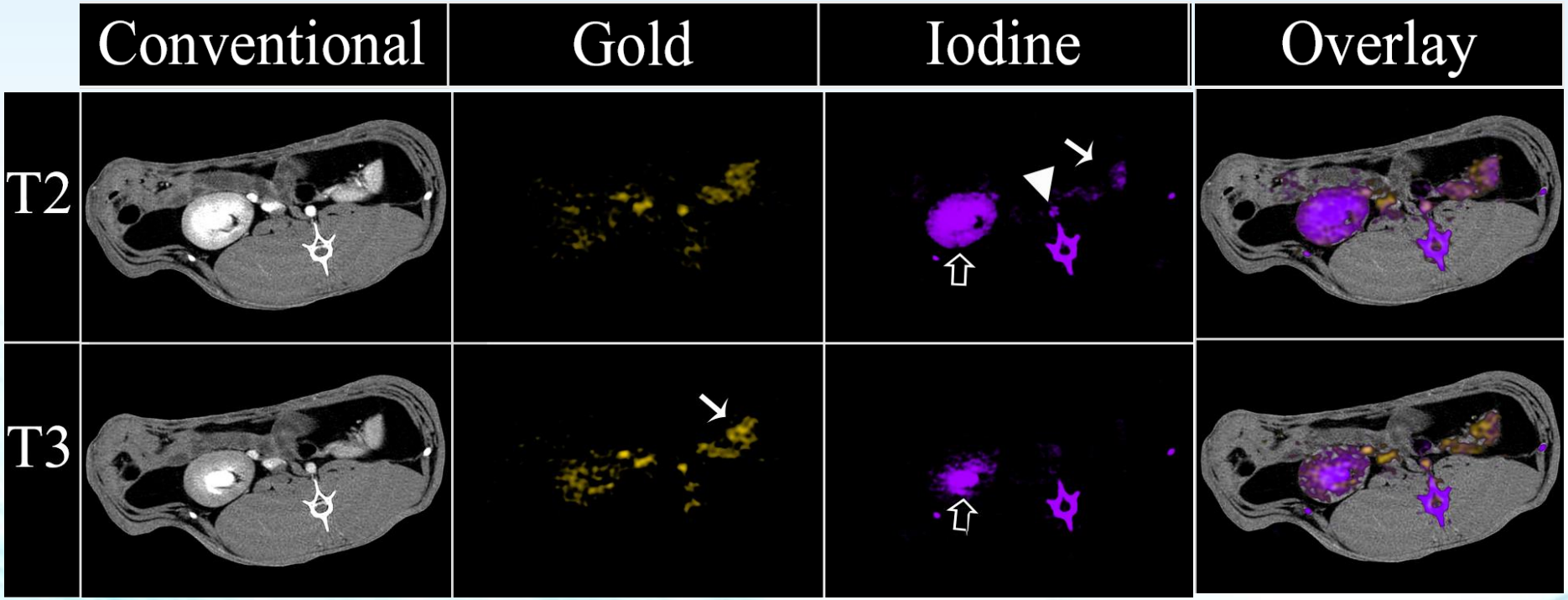
A proposed CT contrast agent using carboxybetaine zwitterionic tantalum oxide nanoparticles: Imaging, biological, and physicochemical performance
Invest Radiol. ;51(12):786-796.

FitzGerald PF

GOLD NANOPARTICLES in vivo

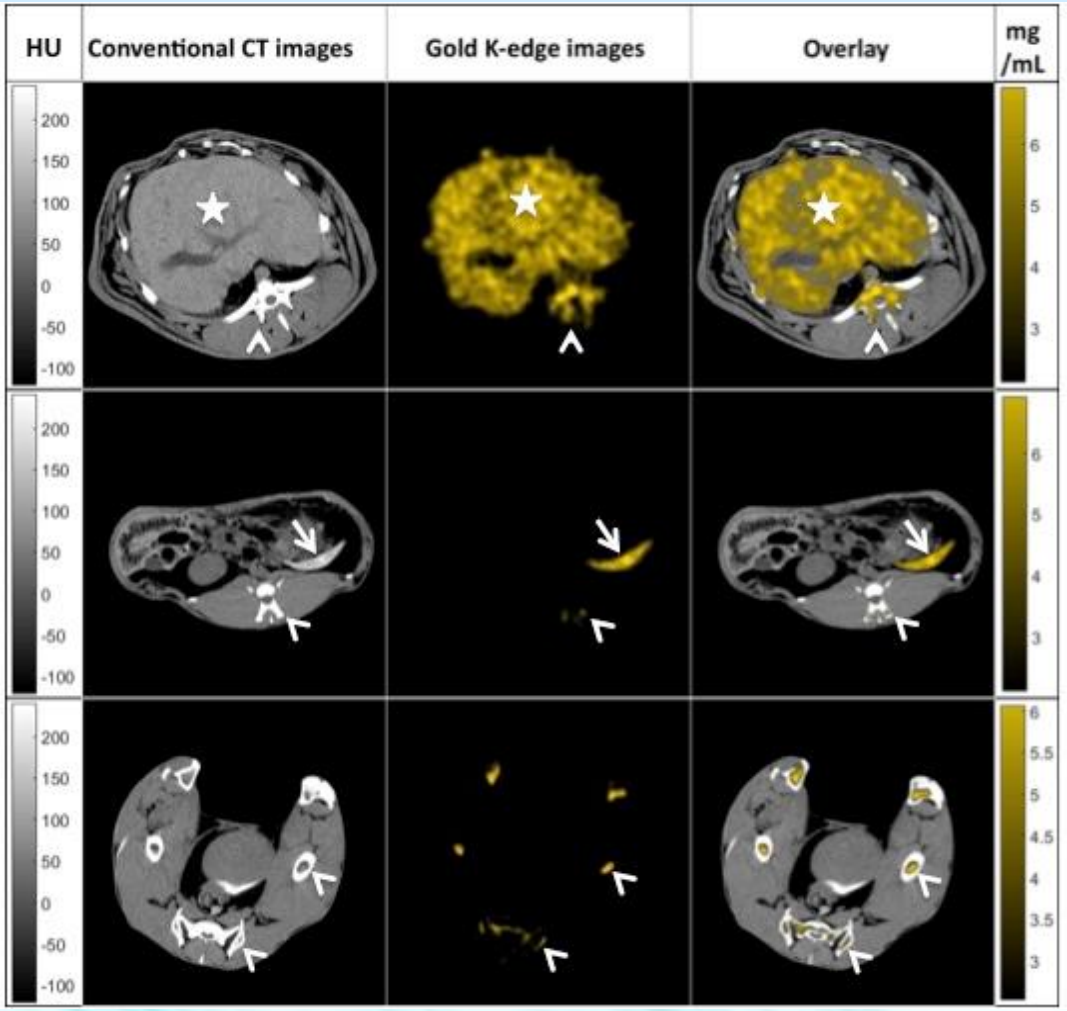
- Injection of Au nanoparticles :
  - Blood pool agent
  - Concentration : 65 mg/mL Au
  - Images at 10 et 35 minutes





Si-Mohamed S et al. Sci Rep. 2017 Jul 6;7(1):4784.

GOLD NANOPARTICLES in vivo

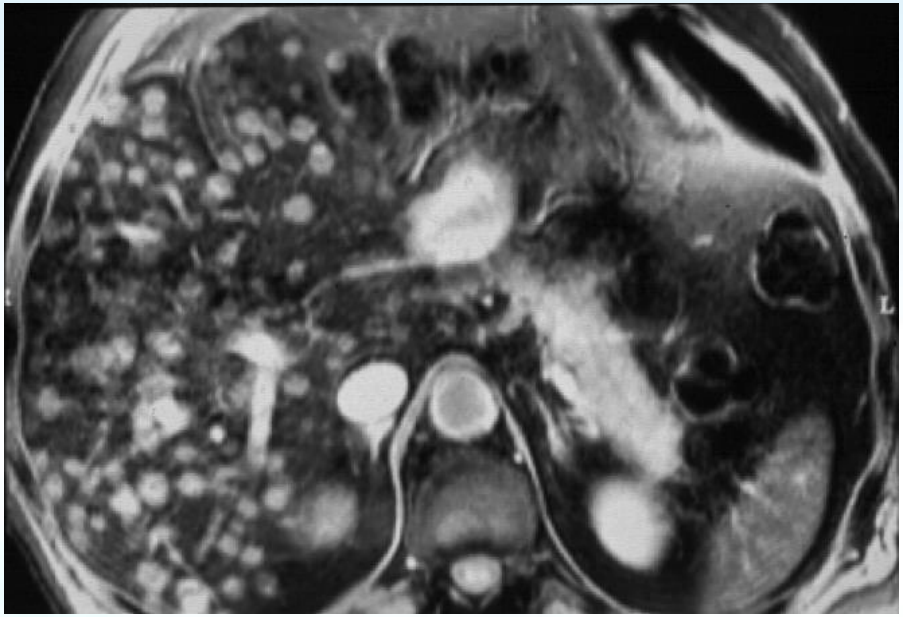


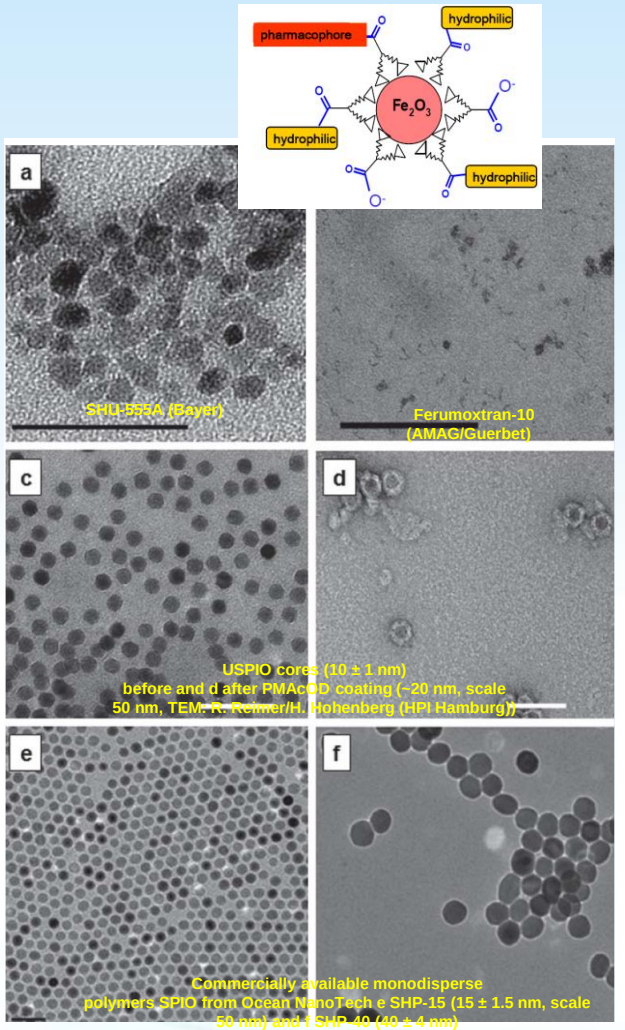
One Month Follow-up

Liver Spleen uptake

Si-Mohamed S et al. Sci Rep. 2017 Jul 6;7(1):4784.

MRI CONTRAST AGENTS

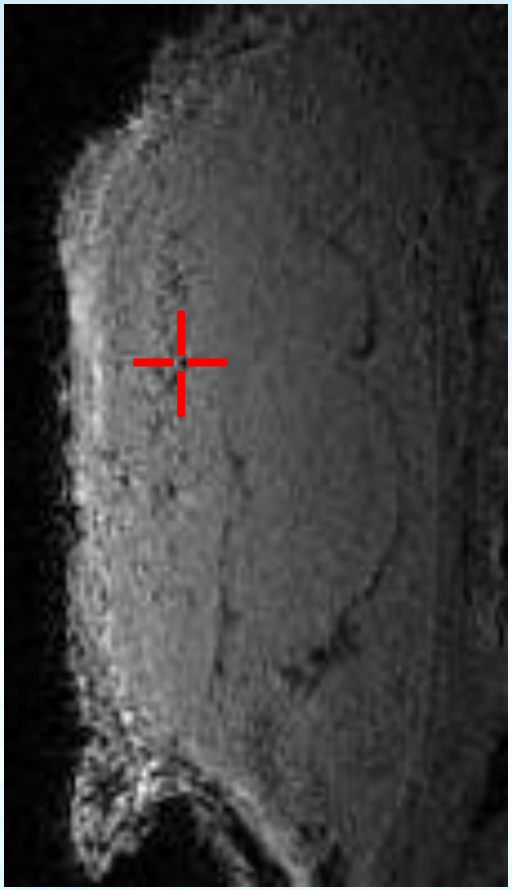


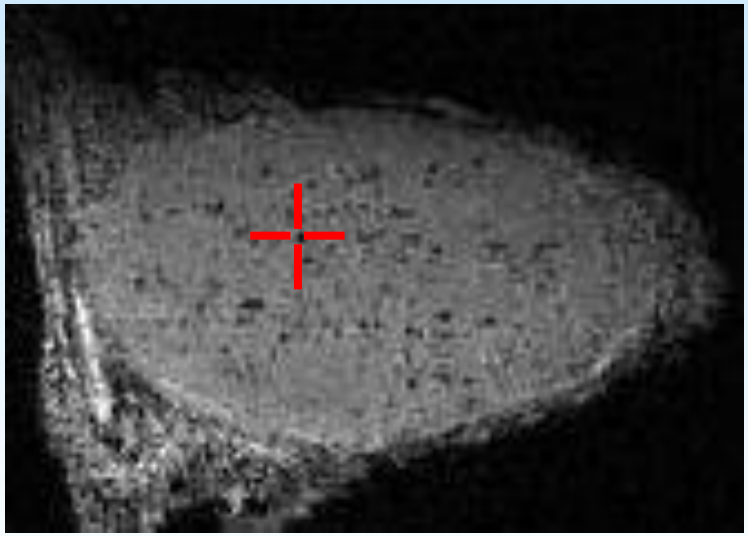


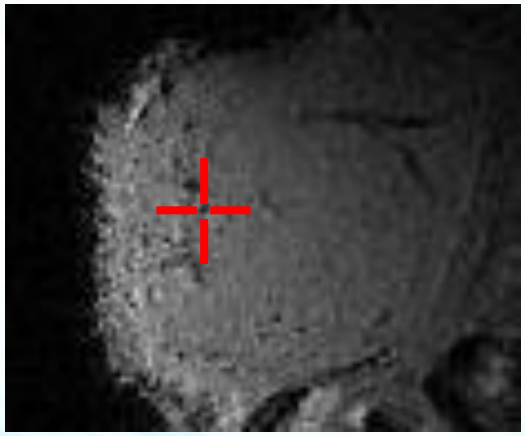
H Ittrich et al. Fortschr Röntgenstr 2013

In vivo single cell detection at 1.5 T

3D punctual hyposignals ➔ labelled lymphocytes (<1 pg Fe /cell) in the tumour







Possibility of detecting cells which divide in vivo and migrate towards homing sites

(voxel size = 59 µm^3, TE = 14 ms tps. acq. = 29 min)

Smirnov et al, Magn. Res. Med, 2008

Iron Oxide Nanoparticles as MR Contrast Agents

- Current record is very disappointing
- At present, only one of such NPs clinically available on the US market for the treatment of iron deficiency (ferumoxytol) (no longer authorised in EU)
- Clinical development of feruglose, ferucarbotran S, ferumoxtran-10 and VSOP stopped
- Very complex and expensive clinical trials

Gd BASED CONTRAST AGENTS

- Initial excellent safety records, **but**

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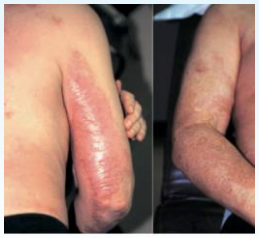
EClinicalMedicine
Published by THE LANCET

Research Paper

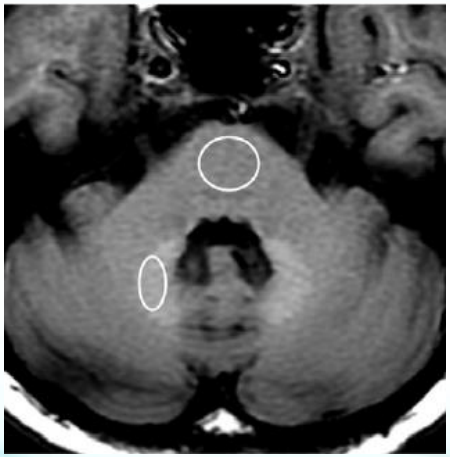
Immediate Hypersensitivity to Contrast Agents: The French 5-year CIRTACI Study

Olivier Clement [a,b,*], Pascale Dewachter [c], Claudie Mouton-Faivre [d], Camille Nevoret [e], Laurence Guilloux [f], Evelyne Bloch Morot [g], Sandrine Katsahian [h], Dominique Laroche [i,j], the investigators of the CIRTACI study , Martine Audebert [1], Béatrice Benabes-Jezraoui [3], Yves Benoit [4],

- Severe Hypersensitivity reactions



- 2007 : Nephrogenic Systemic Fibrosis
- 2014 : Brain Hypersignals
  - EMA linear withdrawn
  - FDA linear warning

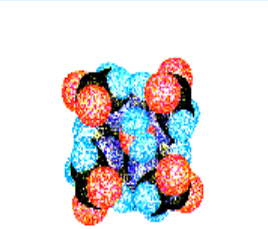


Gd BASED CONTRAST AGENTS

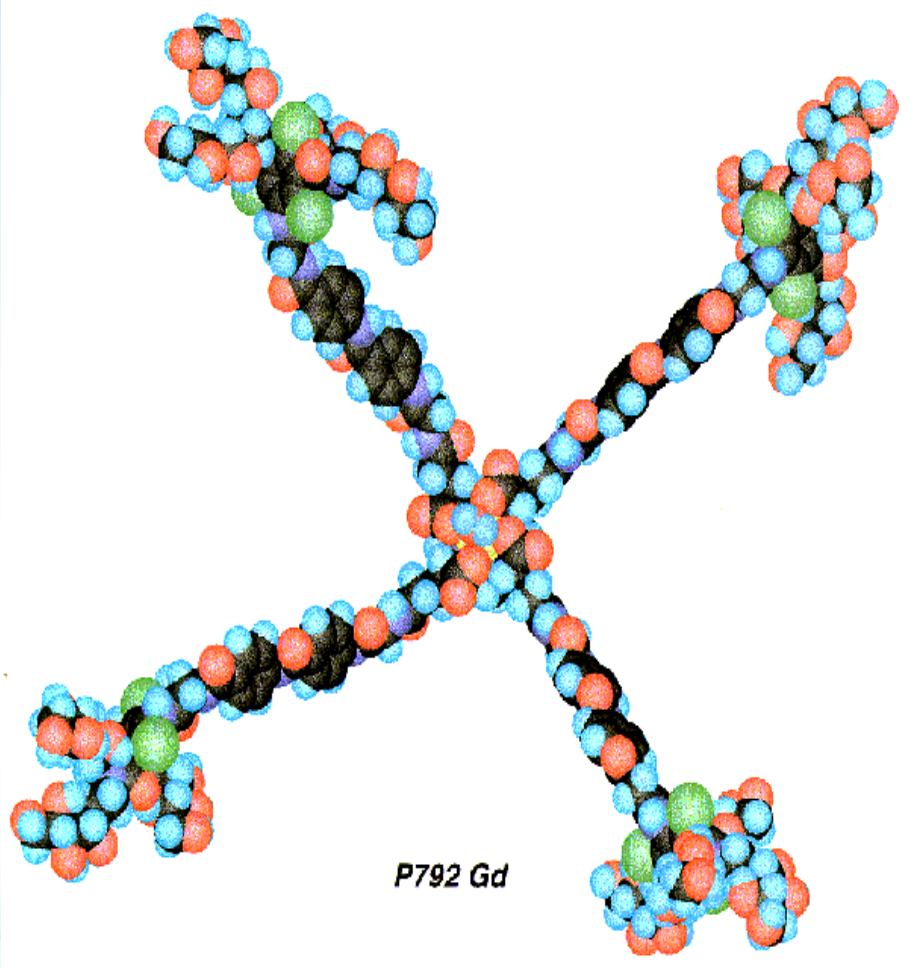
- Decrease the dose
  - Increase relaxivity
  - Without protein binding

- Change the metal
  - Manganese ?
  - Iron ?

Gd BASED CONTRAST AGENTS



DOTA Gd



P792 Gd

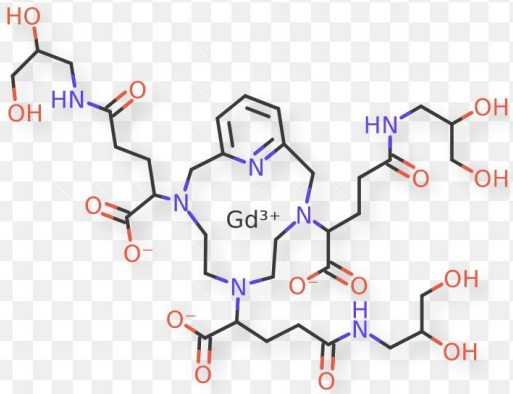
Gadopiclenol: A Novel High-Relaxivity GBCA Under Clinical Development

REVIEW ARTICLE

Advocating the Development of Next-Generation High-Relaxivity Gadolinium Chelates for Clinical Magnetic Resonance

Val M. Runge, MD and Johannes T. Heverhagen, MD, PhD

P03277 is a low-molecular-weight (0.97 kDa) single Gd-based contrast agent from Guerbet with a dedicated 3D design to increase the hydrodynamic size of the complex (patent number EP 1931 673 B1, page 8, example 2).[80] As noted previously, this reduces the molecular tumbling rate, leading to improved interaction with water protons and thus increased T1 relaxivity (with R_1 at 1.5 T being 12.8 and at 3 T 11.6 $mmol^{-1}$ L s^{-1}).[80] In addition, water access to the Gd ion is improved, with a hydration number of 1.7. The approved conventional

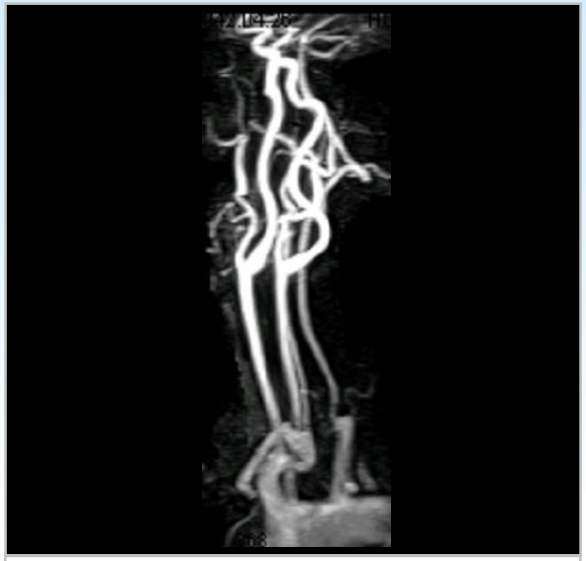


Runge & Heverhagen, Invest Radiol 2018; 381-389

Phase 1 and 2

Toward Molecular Imaging?

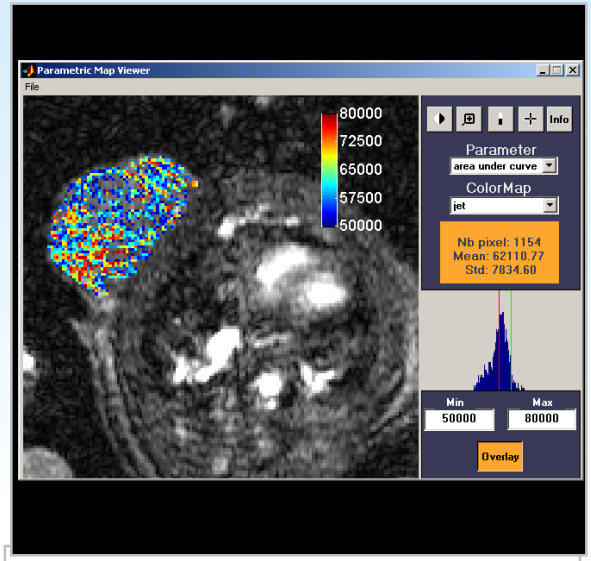
- Medical imaging: toward a more specific approach of pathophysiology



- Anatomical imaging

1st generation of CA

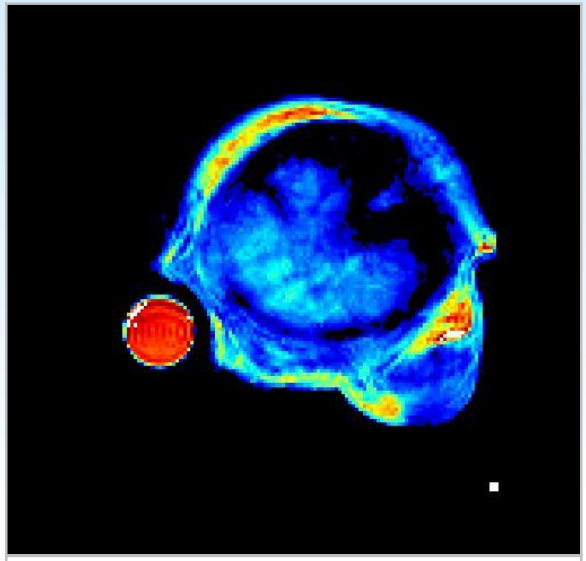
- organs
- Shape/ size of organs
- Location of lesions



- Functional imaging

2nd generation of CA

- Dynamic imaging
  - of organs : heart (contractility), articulations
  - Of flows : blood (perfusion with CA, ASL), vascular permeability (intra → extravascular flow, DCE-MRI)
  - of blood volume

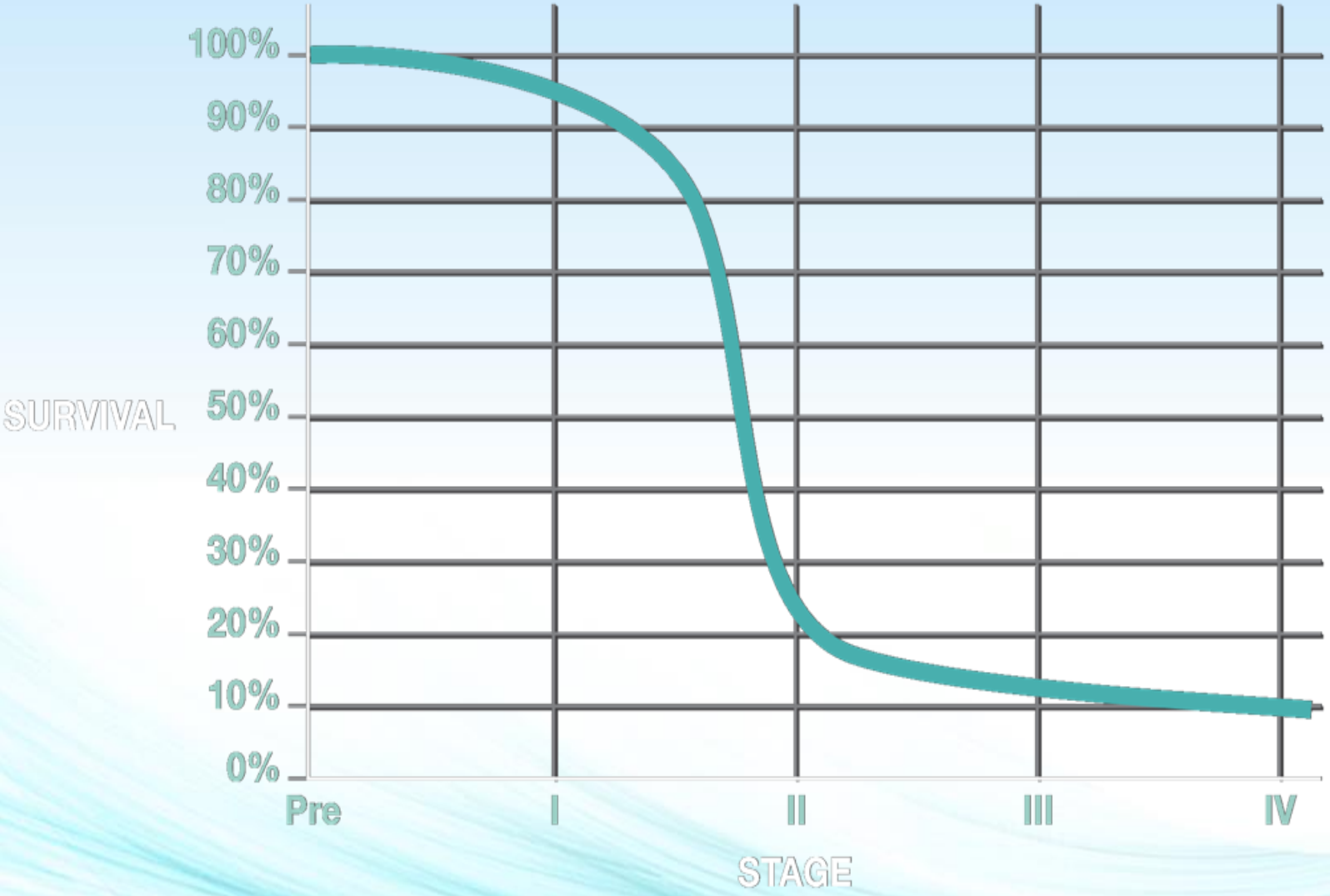


- Molecular imaging

3rd generation of CA

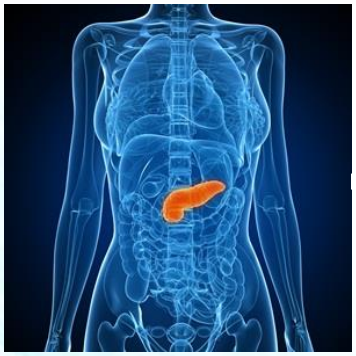
- Imaging of receptors/transporters : $\alpha_v\beta_3$, VCAM, PS, folate
- Imaging of metabolic systems: FDG, etc.
- Neurotransmitter imaging: ^{18}FDOPA, etc.

Early Cancer Detection



- CEA
- Suppressors of Cytokine Signallng (SOCS2 and SOCS6)

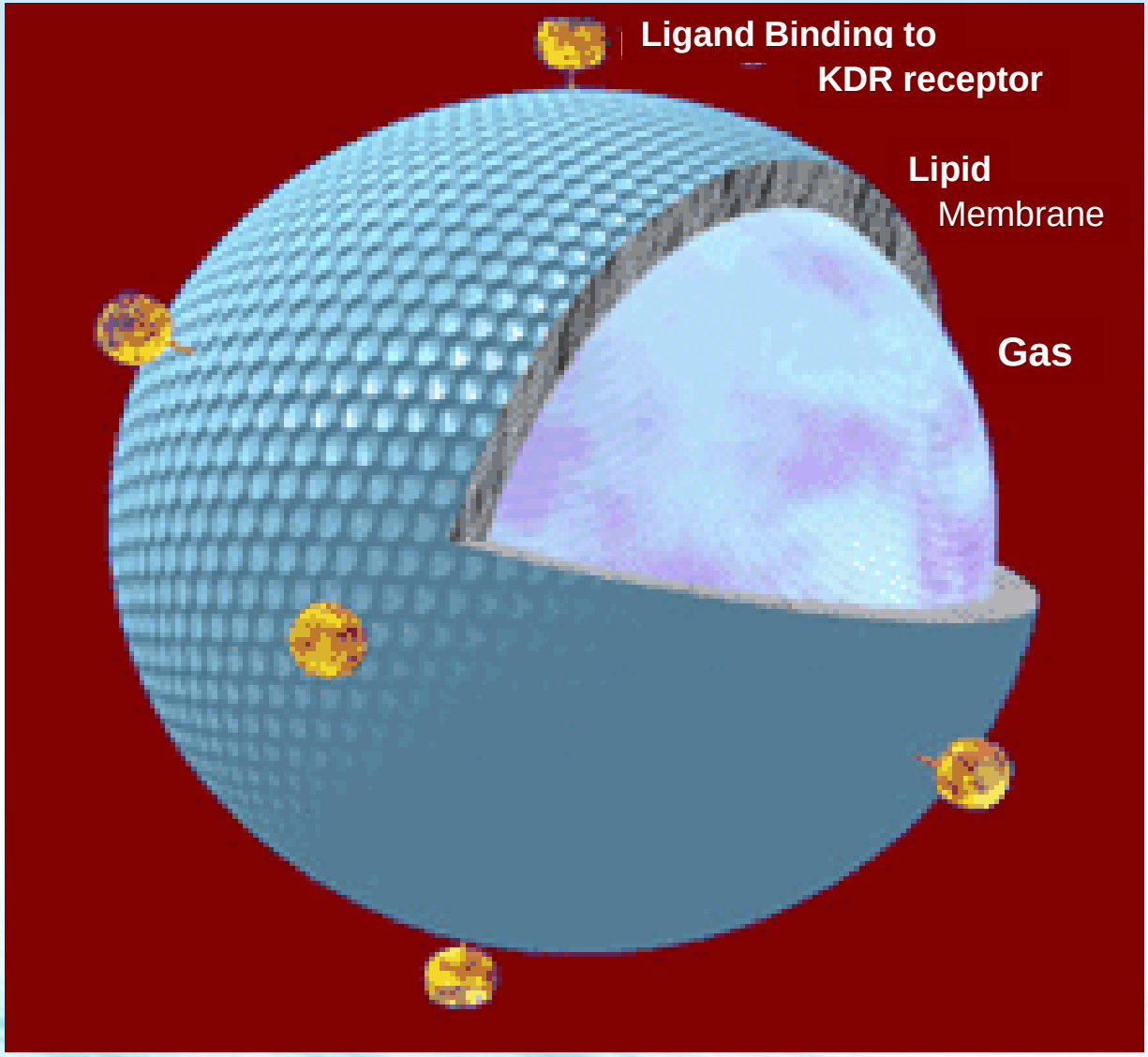
- Prostate-specific kallicreins
- ERG protein
- ERG gene
- PCA3 gene
- …….



- CA19-9
- Cyclophilin B
- Glypican-1
- Urinary proteins LYVE1, REG1A and TFF1
- …….

- AFP
- AFP L3
- Golgi protein 73
- Dickkopf-1 (DKK1)
- Midkine (MDK),
- …….

VGFR (KDR) -Targeted Microbubble (BR55)



A Contrast Agent for Molecular Imaging Will Most Likely be Developed/Used as a Biomarker

Table 2. Different sources of biomarkers.

Method	Advantages	Disadvantages
Molecular imaging	Non-invasive and allows for serial assessment in time Overcomes the problem of tumor heterogeneity within and between tumor lesions Takes target availability into account	Only one marker per scan Requires extensive tracer validation before clinical use Limited availability compared to, e.g., immunohistochemistry
Tumor biopsy	Multiple markers can be examined on one biopsy Several types of biomarkers can be analyzed (protein, RNA, DNA) Easy applicable in multiple centers	Sampling error due to heterogeneity within a tumor and between a tumor Invasive, thus not preferred for repeated assessment
Blood/plasma	Easy access Allows repeated analysis Different types of biomarkers can be analyzed (blood chemistries, proteins, RNA, DNA, circulating tumor cells)	No necessarily representative for processes occurring in the tumor

S Heskamp et al., Exp Opin Drug Deliv 2014

If Imaging Biomarker: Pandora's Box

- Scientific/technical Clinical validation

- Can the contrast agent be qualified of companion biomarker? If yes, please demonstrate:
  - The relevance of the BM-based therapeutic strategy
  - A BM/treatment interaction (treatment depends on the + or – response of the BM)
  - Efficacy of treatment in BM+ patients

- Specific challenges:
  - Robust and standardised procedures (images acquisition and treatment)
  - Need for regulatory approvals for the devices and softwares used in the development process
  - Procedure available in multiple centres (ideally not just specialised centres)
  - Correlation with pathology

CHALLENGES

- REGULATORY
  - Long and expensive clinical trials
  - Specific of drug regulation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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European Medicines Agency

Final report on the adaptive pathways pilot

Summary

In March 2014 EMA launched a pilot project to explore the adaptive pathways approach, a scientific concept of medicines development and data generation intended for medicines that address patients' unmet medical needs.

CHALLENGES FOR A COMPANY

- REGULATORY
- CHEMICAL SYNTHESIS SCALE UP
- CLINICAL TRIALS
- FINAL PRICING

Crucial

Net Present Value (NPV) is the difference between the present value of cash inflows and the present value of cash outflows. NPV is used in capital budgeting to analyze the **profitability of a project.**

The formula for calculating NPV:

$$NPV = \sum_{t=1}^{T} \frac{C_t}{(1+r)^t} - C_o$$

In short: NPV should be bigger than project cost!

where

Ct = net cash inflow during the period t

Co = total initial investment costs

r = discount rate, and

t = number of time periods

CONCLUSION

- Future in Research : YES
  - Photo counting Scanners will be an opportunity to develop new non Iodine based agents
  - Non Gd agents
  - Gado-New Agents (high-relaxivity, macrocyclic
  - Ultrasound (US)
  - Mol imaging

- BUT: developing costs and regulation burdens