

Non invasive specific macrophage spectral photon counting CT K-edge imaging in atherosclerosis using pegylated gold nanoparticles

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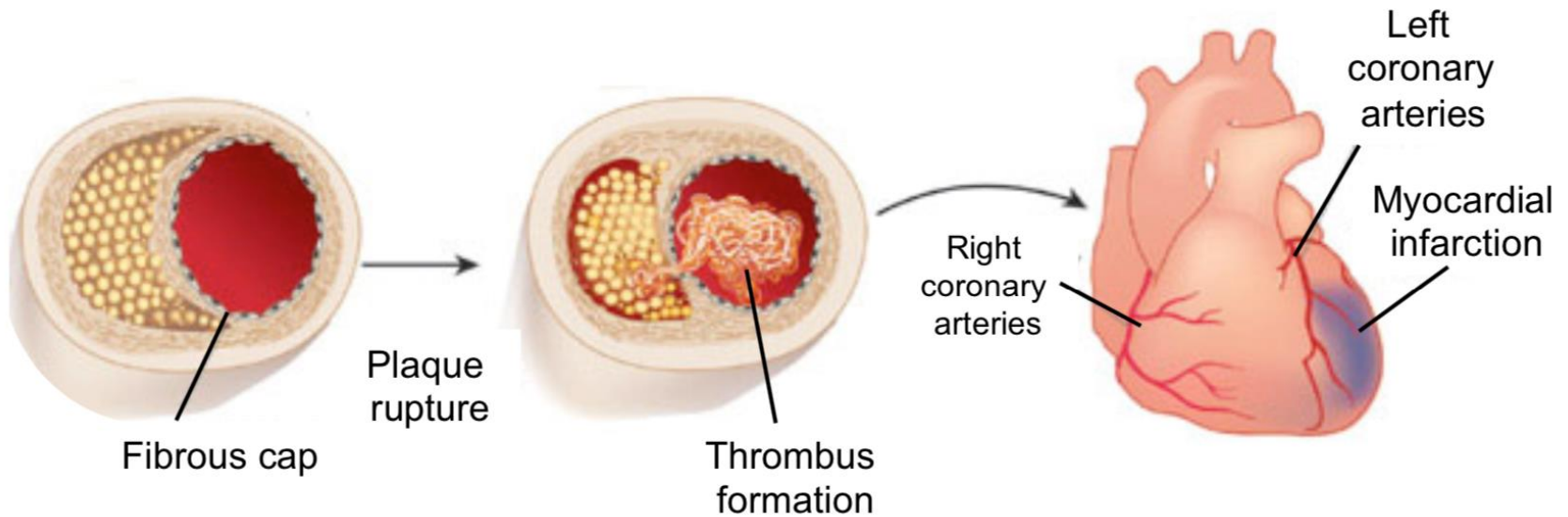
***** Philips research, Haifa, Israel



5th Workshop on Medical Applications of Spectroscopic X-ray Detectors

13-16 mai 2019
CERN

Atherosclerosis



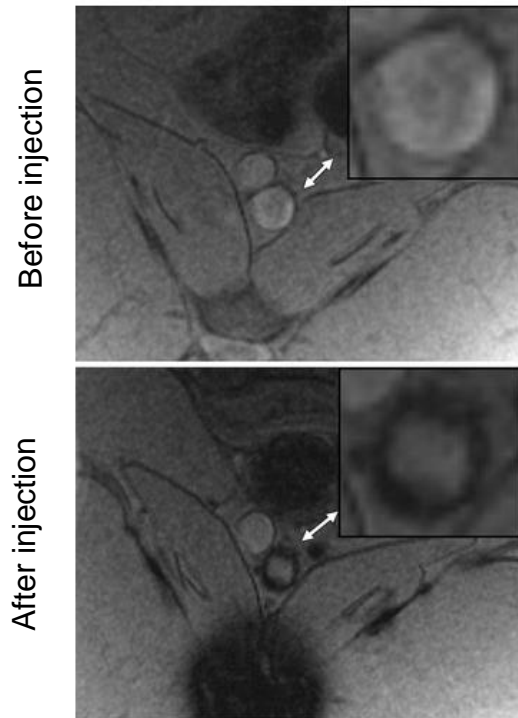
Vulnerable plaque:

- High **macrophages** infiltration
- Thin fibrous cap

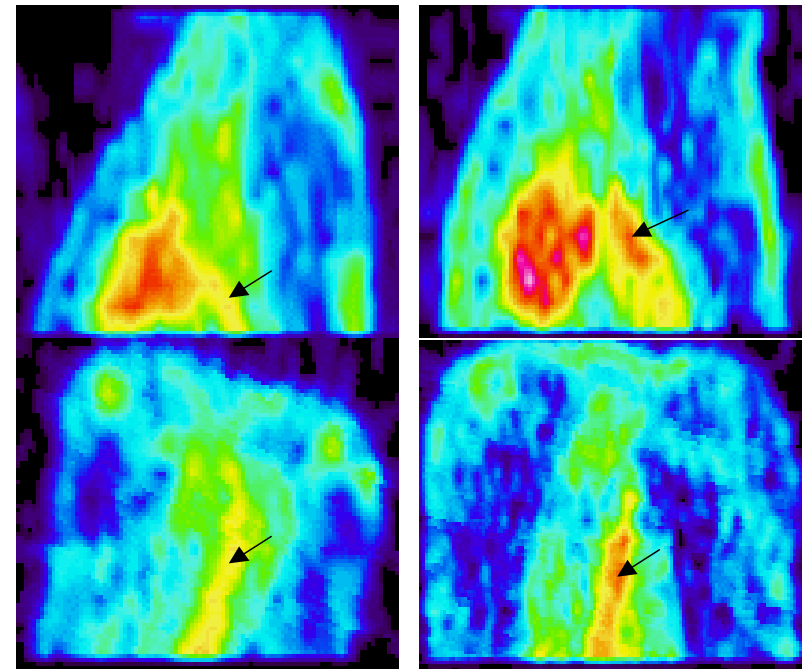
Need for imaging the **macrophage burden** within the vessels

Macrophage imaging

- MRI combined with iron oxides (P904)



- Positron emission tomography (PET) combined with ^{18}F -FDG



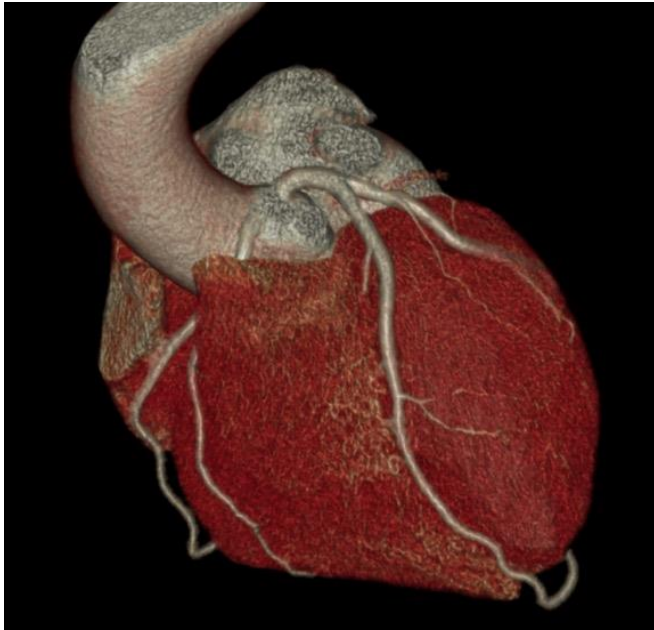
Healthy rabbit

Atherosclerotic rabbit

Limitations for **coronary arteries diseases (CAD)** imaging

CT Coronary imaging

Computed tomography is an excellent modality



Current CT limitations:

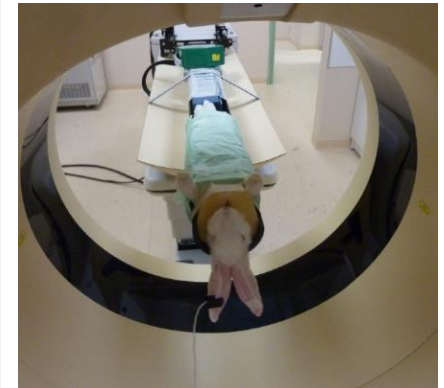
- Spatial resolution for detailed analysis of the plaque and the lumen
- Contrast resolution for detailed analysis of the plaque components

Need for **improved** CT performances

SPCCT prototype

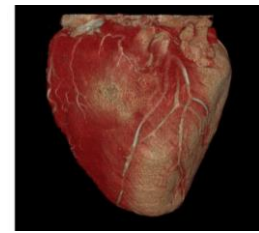
Pre-clinical Photon Counting Spectral CT (SPCCT) prototype

Parameter	Animal Prototype Specifications
Platform	Philips iCT
Tube voltage [kVp]	120
Tube current [mA]	100
Physical focal spot size [mm x mm]	0.6 x 0.7
Gantry rotation time [s]	1
In-plane field-of-view [mm]	168
Physical detector size [$\mu\text{m} \times \mu\text{m}$]	500 x 500
Pixel size at iso-center [$\mu\text{m} \times \mu\text{m}$]	275 x 275
z-coverage at iso-center [mm]	2.5
Number of detector pixels	616 x 9
Readout electronics	Philips ChromAIX2 ASIC
Number of energy thresholds	5
Sensor material, thickness	CZT, 2 mm



Philips SPCCT pre-clinical prototype*

SPCCT for coronary imaging

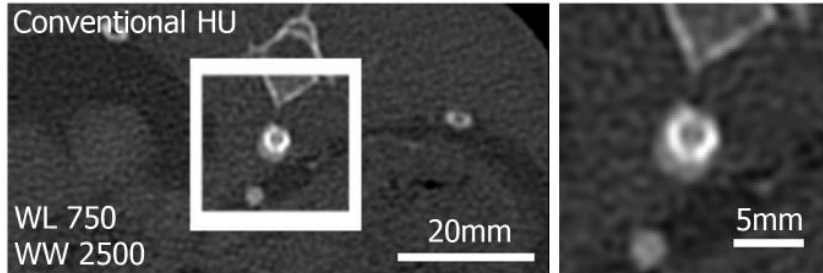


High spatial resolution modality combined with **K-edge** imaging

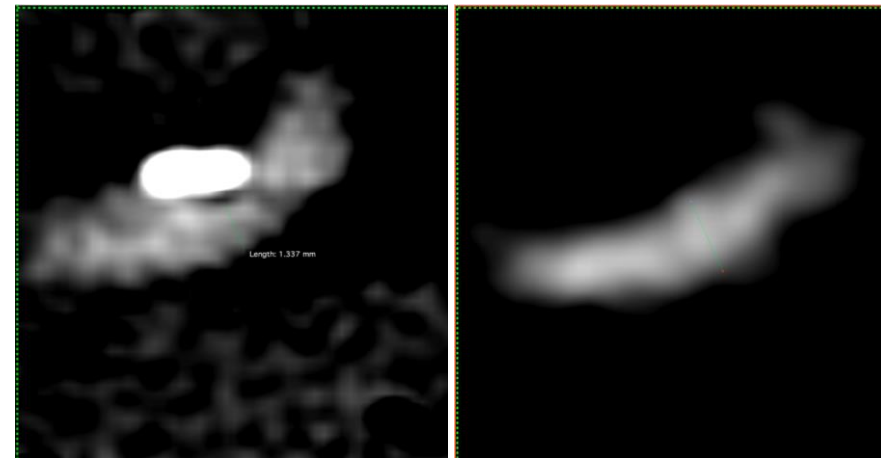
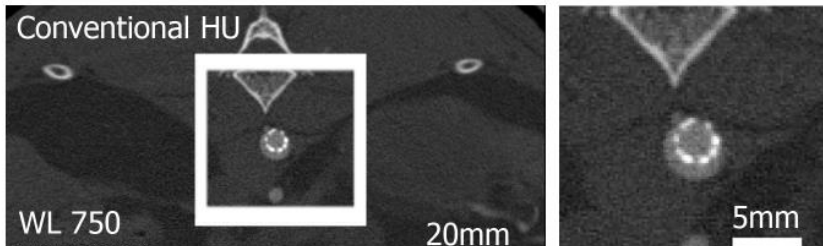
- Stent imaging
- Coronary gadolinium K-edge imaging

CORONARY BLOOD FLOW

B64



SPCCT



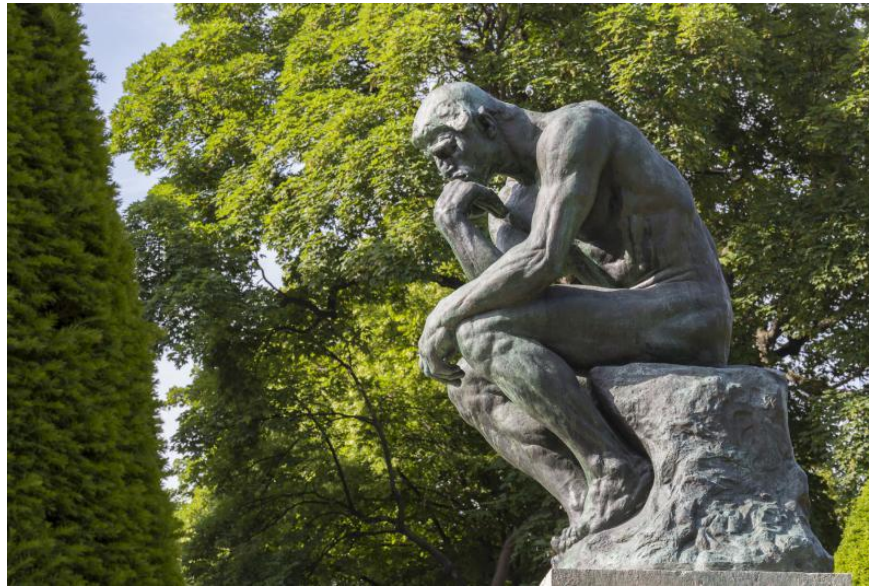
Need for **specific plaque imaging** with SPCCT

SPCCT for atherosclerosis imaging

Improved contrast resolution

Improved spatial resolution

Specificity of the K-edge technique



Need for a **K-edge** element contrast agent based for **lumen and plaque** with potential for **macrophage targeting**

Gold nanoparticles (AuNP)

- Pegylated gold nanoparticles
 - Characteristics:
 - capped with thiol-PEG-2000
 - mean hydrodynamic radius of 18 nm
 - concentration: 65 mg/ml of gold
- Strong CT contrast

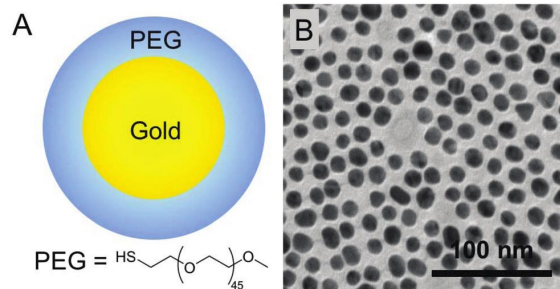
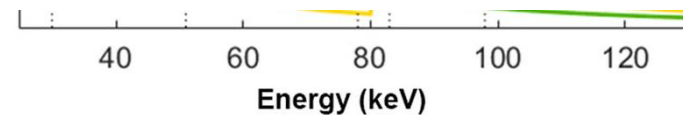


Fig. 1 (A) Schematic representation of the AuNP. (B) Transmission electron micrograph of the AuNP.



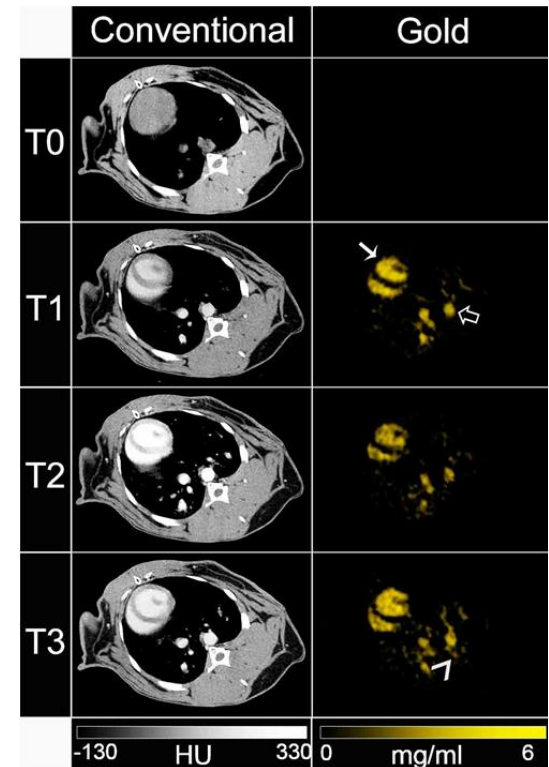
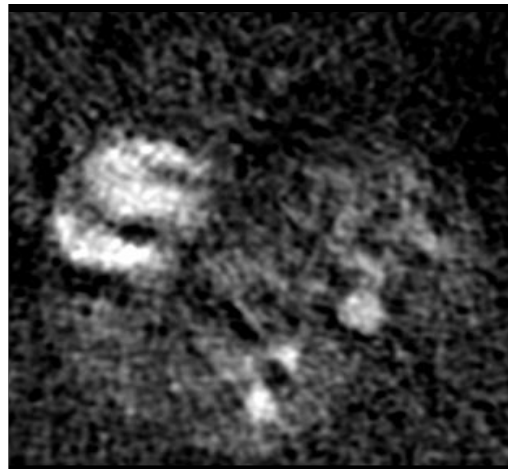
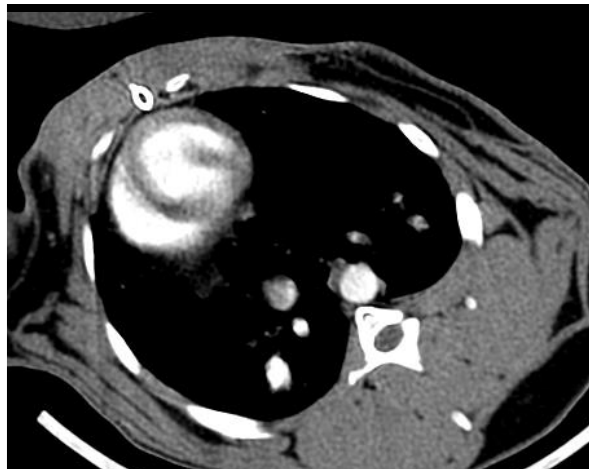
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Potential for **atherosclerosis** imaging ?

Dynamic K-edge imaging

- Dynamic K-edge acquisitions
- Blood pool effect

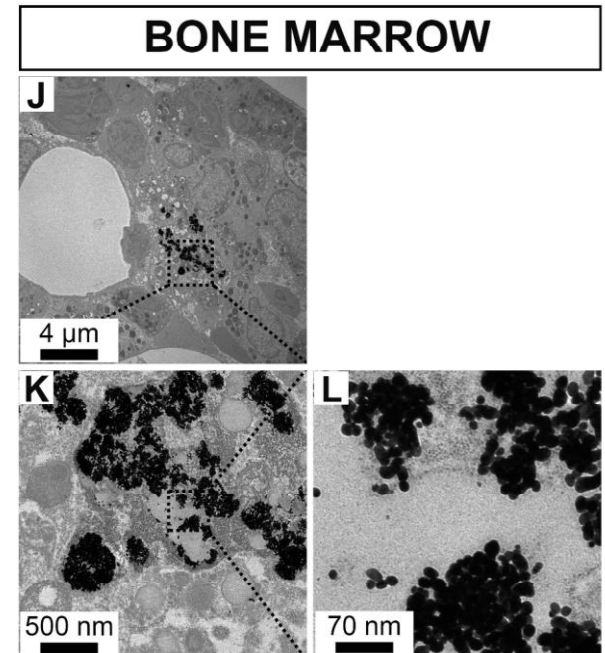
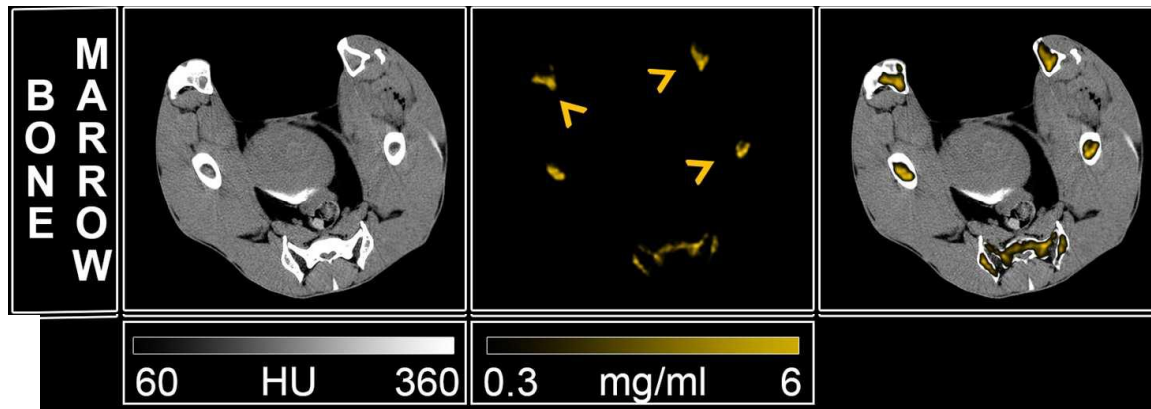


Prerequisite for **lumen** visualization

Macrophage detection (1)

Feasibility of specific **K-edge** in vivo imaging of pegylated-AuNP

- Uptake by the **macrophages**
- High detection of **bone marrow** accumulation

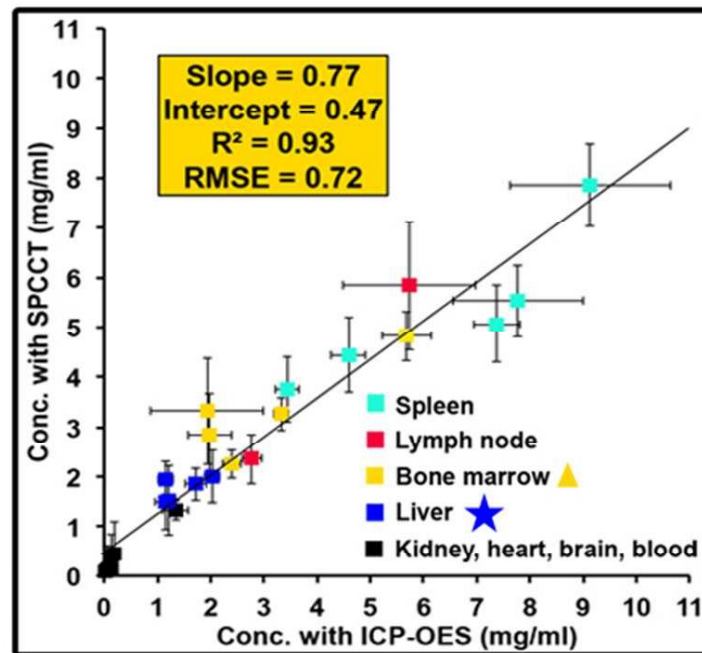


Prerequisite for **macrophage** imaging

Macrophage detection (2)

Feasibility of **quantitative** in vivo imaging of pegylated-AuNP

- Excellent correlation with ICP analysis



Prerequisite for a quantitative macrophage analysis within an **atherosclerotic disease** model

Objective of the present study

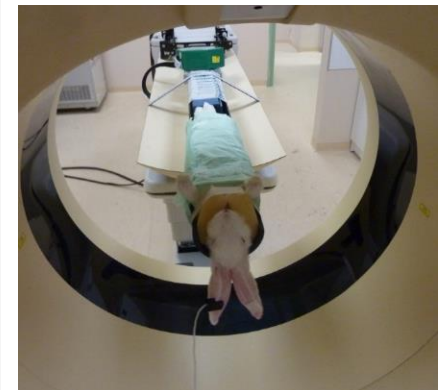
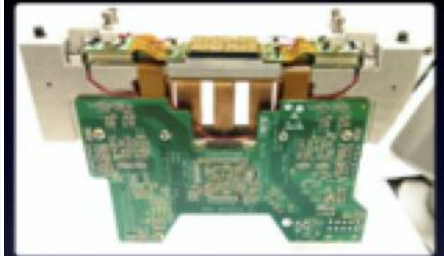
Detect and quantify the macrophages component in vivo within the atherosclerotic plaques via K-edge imaging

SPCCT system

Pre-clinical prototype SPCCT

Parameter	Animal Prototype Specifications
Platform	Philips iCT
Tube voltage [kVp]	120
Tube current [mA]	100
Physical focal spot size [mm x mm]	0.6 x 0.7
Gantry rotation time [s]	1
In-plane field-of-view [mm]	168
Physical detector size [$\mu\text{m} \times \mu\text{m}$]	500 x 500
Pixel size at iso-center [$\mu\text{m} \times \mu\text{m}$]	275 x 275
z-coverage at iso-center [mm]	2.5
Number of detector pixels	616 x 9
Readout electronics	Philips ChromAIX2 ASIC
Number of energy thresholds	5
Sensor material, thickness	CZT, 2 mm

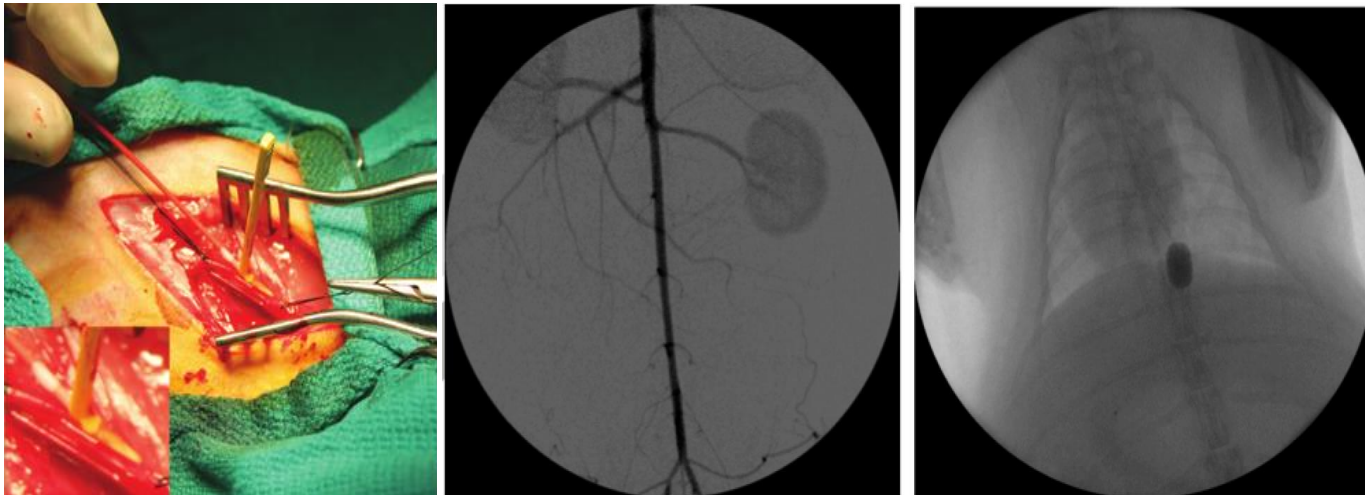
Photon Counting Electronics



Philips SPCCT pre-clinical prototype*

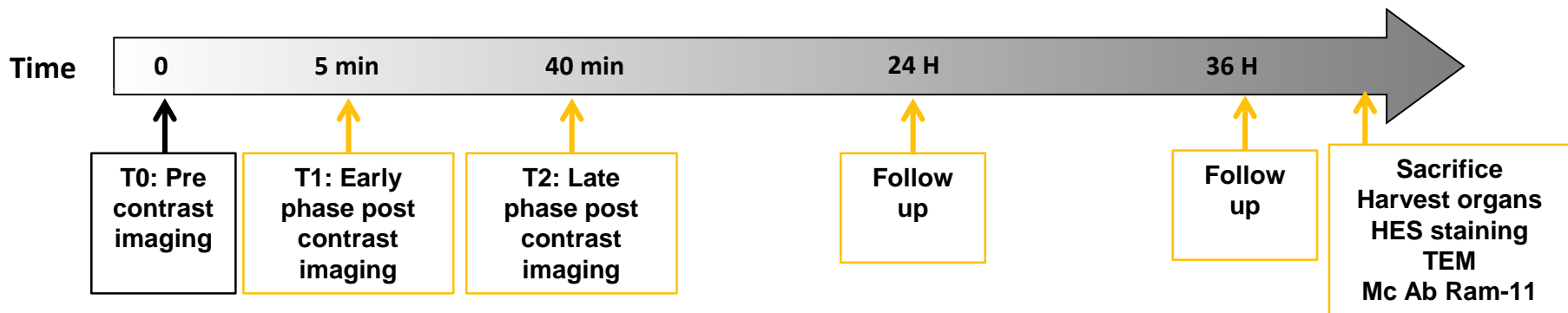
Animal model

- Male New Zealand white rabbits
- High-cholesterol diet (1%) for 6 weeks, followed by normal diet for 6 weeks
- Balloon injury of aorta 2 weeks after starting diet



SPCCT Imaging protocol

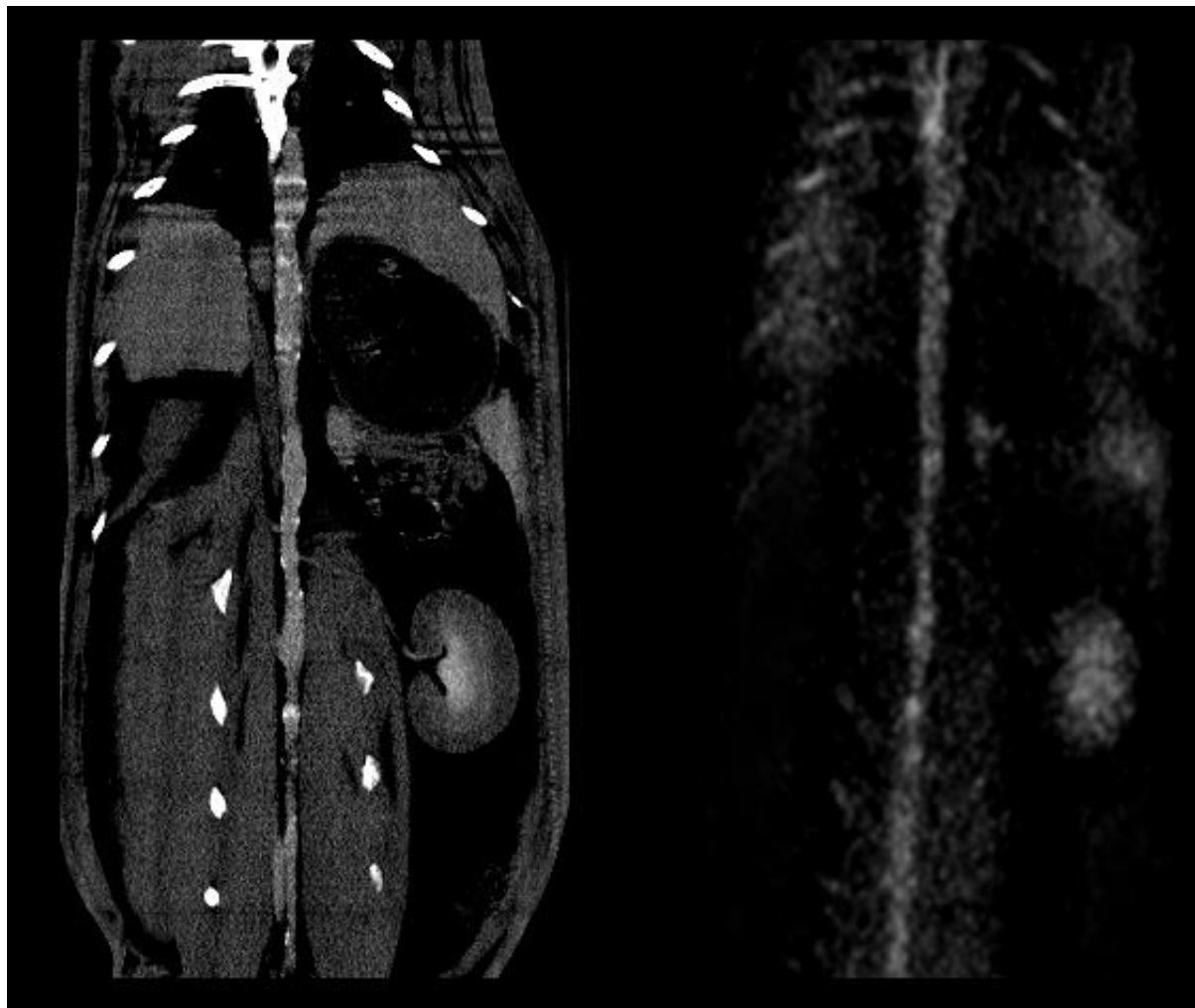
- 7 atherosclerotic and 4 non injured adults NZW rabbits (3.4 ± 0.4 kg)
- Injection protocol: 3.5 mL/kg of AuNP (concentrated at 65 mgAu/mL)
- Imaging protocol:
 - 120 kVp, 100 mAs
 - energy bins set to 30–53, 53–78, 78–83, 83–98, 98–120 keV
 - repetitive acquisitions over 2 days



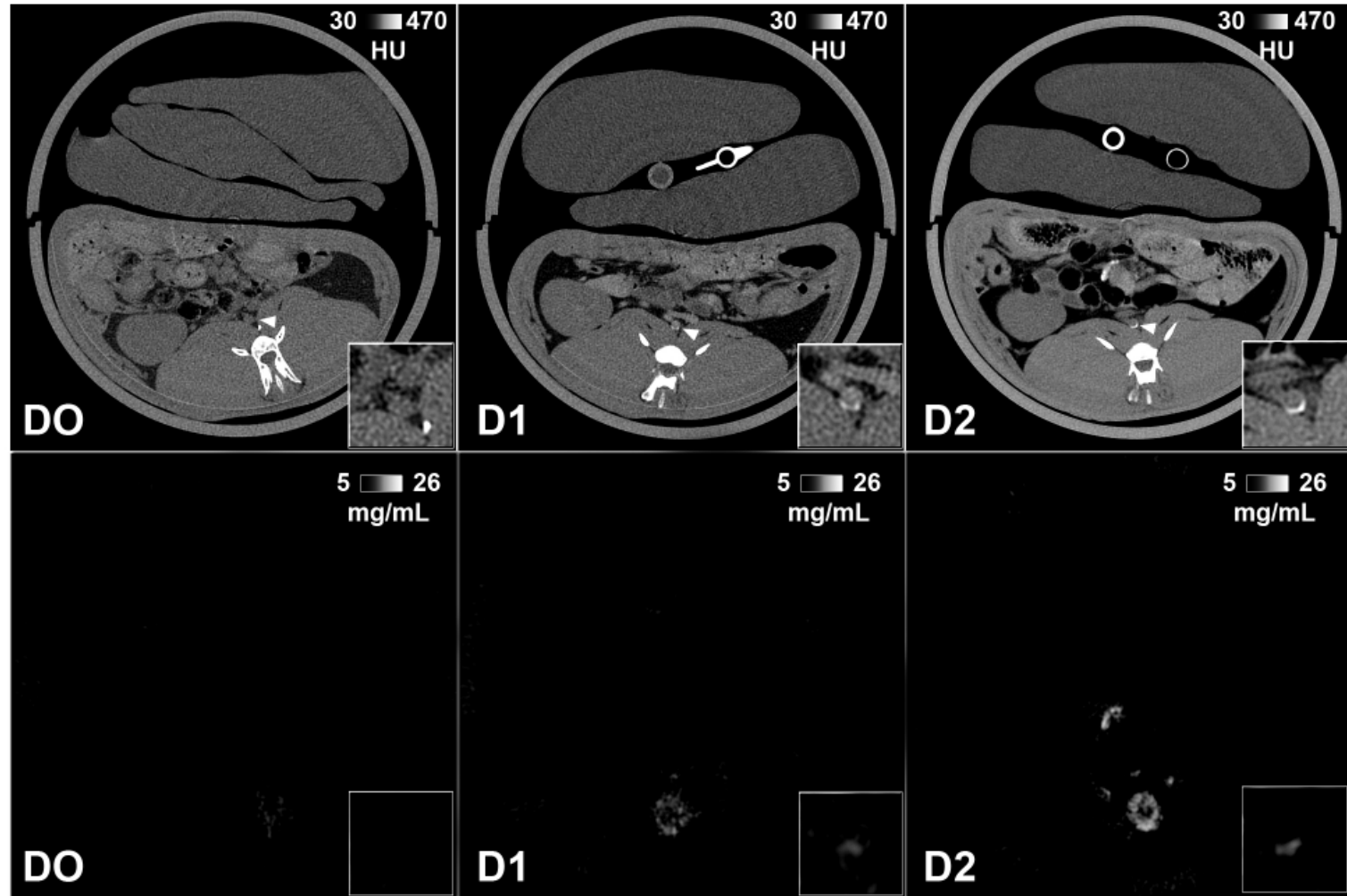
Analysis

- Image reconstruction
 - Conventional images: HU units
 - Specific K-Edge Gold images: mg/ml units
- Image analysis
 - Semi-automatic segmentation of the aorta (Amira; Thermo Fischer Scientific)
 - Segmentation of the inner lumen and parietal wall based on predefined outer number of pixels (3 pixels thickness)(Matlab routine)
 - Quantification of the content of gold in the wall (mg)
- Histological analysis
 - Macroscopic analysis
 - Immunostaining with monoclonal antibody RAM-11
 - Transmission electron microscopy (TEM)
- Inductively coupled plasma-optical emission spectrometry (ICP-OES)
 - Quantity of gold within the aortas

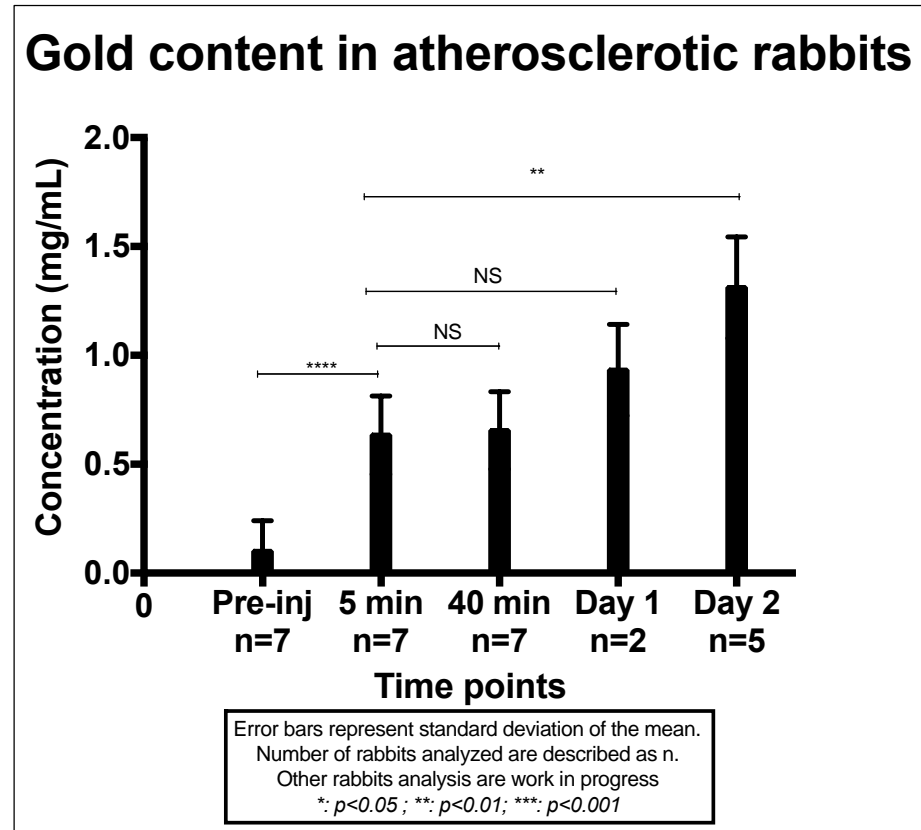
SPCCT imaging



SPCCT imaging



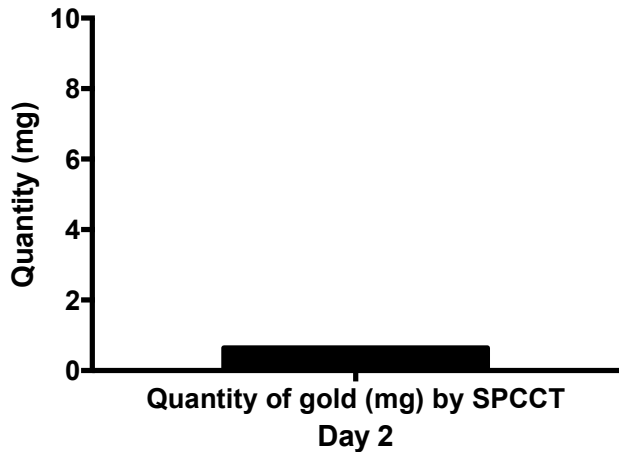
Overall atherosclerotic burden



Significant increase in gold concentration was observed in the atherosclerotic aorta

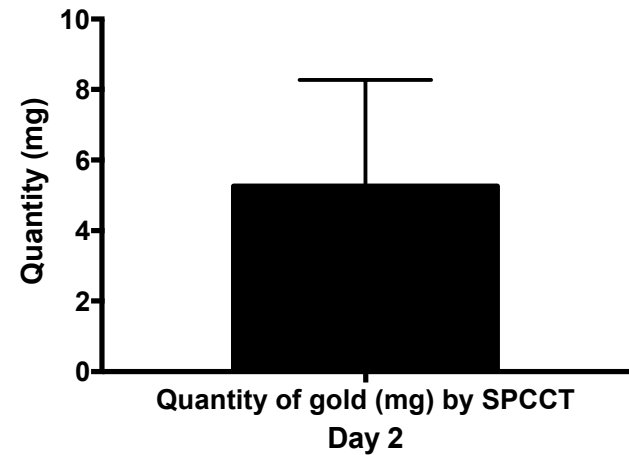
Overall atherosclerotic burden

Quantity of gold (mg) by SPCCT in control rabbits



To be noted that one rabbit has been fully completed.
Other 3 rabbits analysis are work in progress.

Quantity of gold (mg) by SPCCT in atherosclerotic rabbits



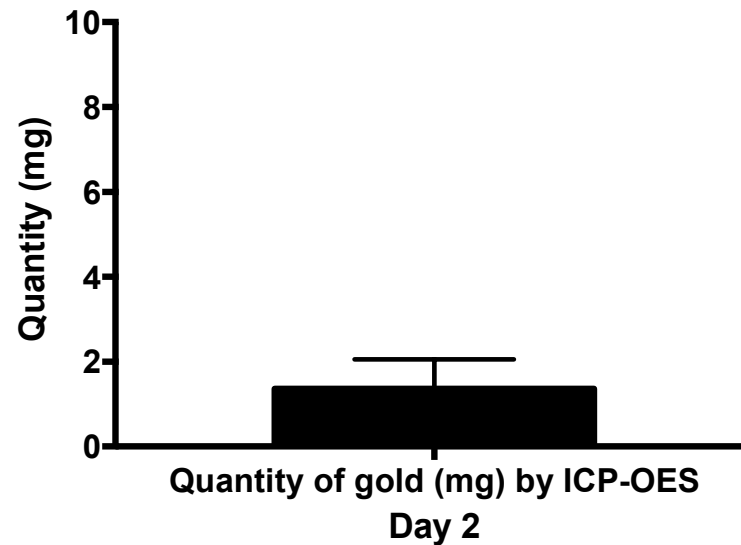
Error bars represent standard deviation of the mean. To be noted that only 5 rabbits have been fully analyzed.
Other 4 rabbits analysis are work in progress.

High quantity of gold was observed within the atherosclerotic aortic wall

Overall atherosclerotic burden



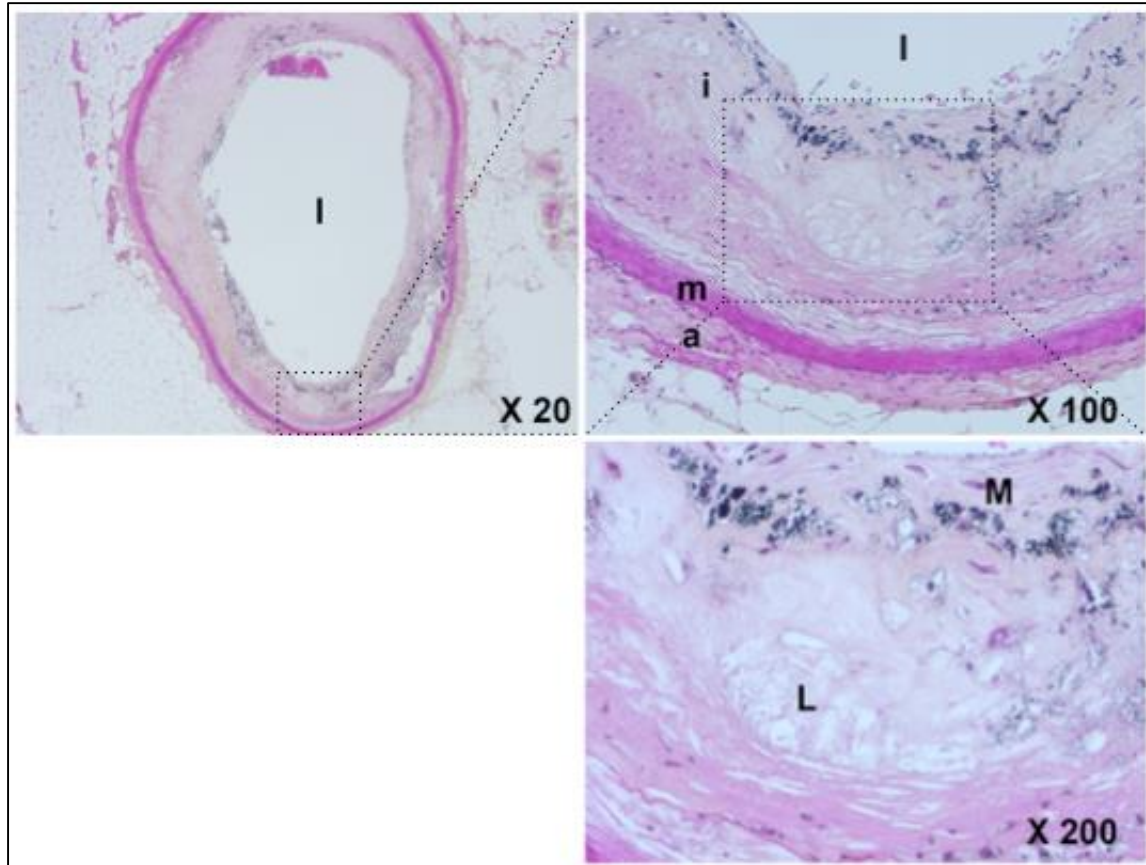
Quantity of gold (mg) by ICP-OES in atherosclerotic rabbits



Error bars represent standard deviation of the mean.
To be noted that all the rabbits have been fully analyzed.

Confirmation of a high quantity of gold

Histopathology imaging

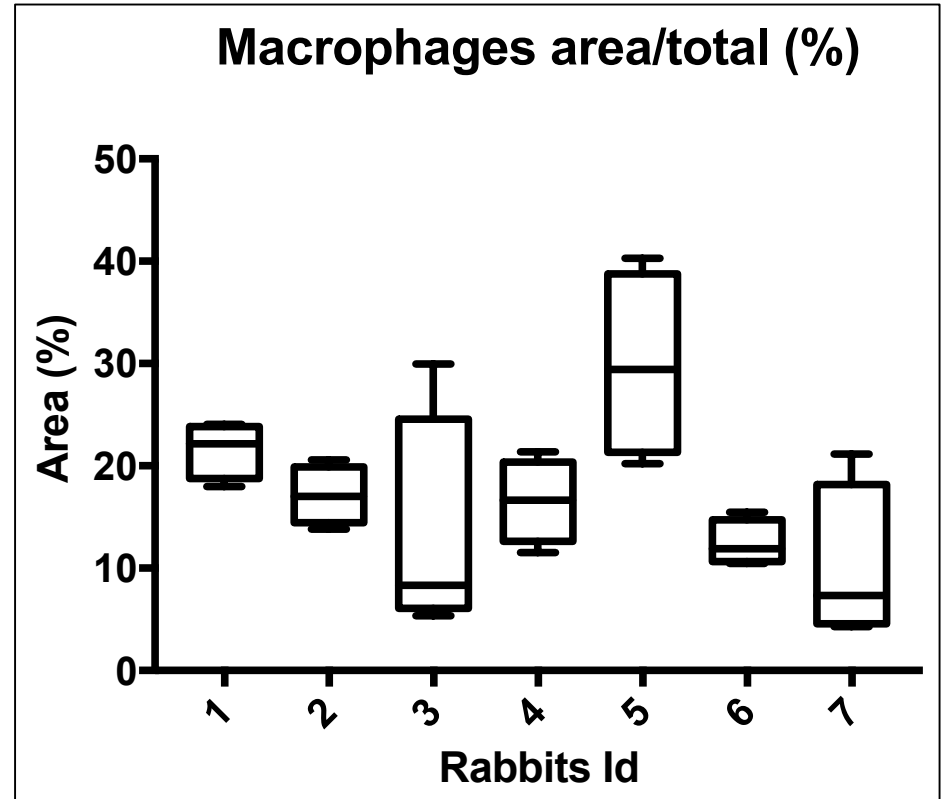


l: lumen
i: intima
m: media
a: adventice

L: lipid core
M: macrophage

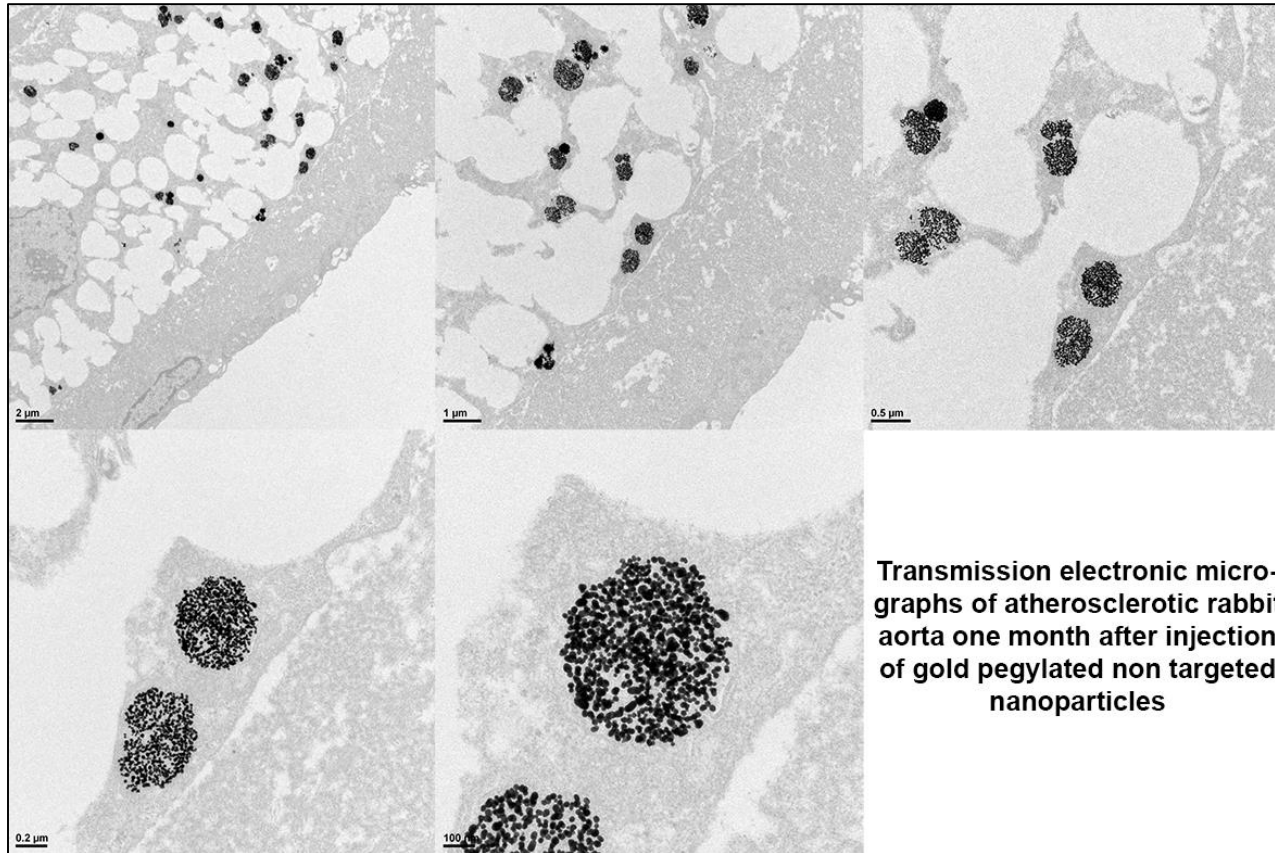
Thick and fibrosed intima rich in inflammatory cells, mainly macrophages, foam cell with lipid core and calcifications

Immunostaining imaging



High proportion of **macrophages** within the plaque

TEM imaging



Uptake of gold nanoparticles with the **macrophages**

Conclusion

- PEG-AuNP accumulates in rabbit macrophages
- SPCCT can **detect** and **quantify** specifically PEG-AuNP in atherosclerotic rabbits with K-edge imaging

=> Potential to **image vulnerable plaque with SPCCT**

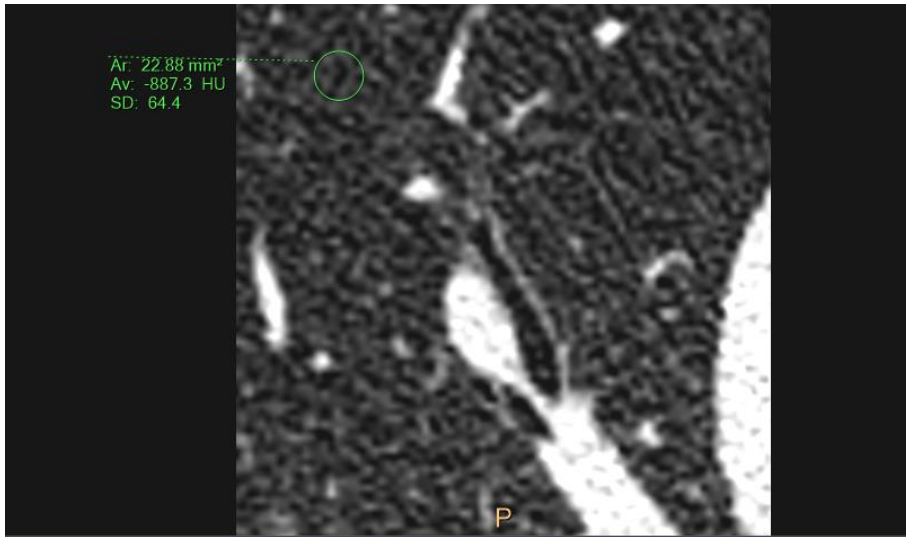
Perspectives

Parameter	Phantom scanner specificity
Base Platform	iCT
Tube Voltage	120, 140 kVp
Tube Current	10-300 mA
Spatial Resolution	> 20 lp/cm
Anti-scatter grid	1x1 mm ²
Pixel size	0.25*0.25 mm
Z-Coverage at isocenter	17.6 mm
FOV	500 mm
Minimum Rotation Time	0.33 sec/rotation
Acquisition Modes	Axial, Helical

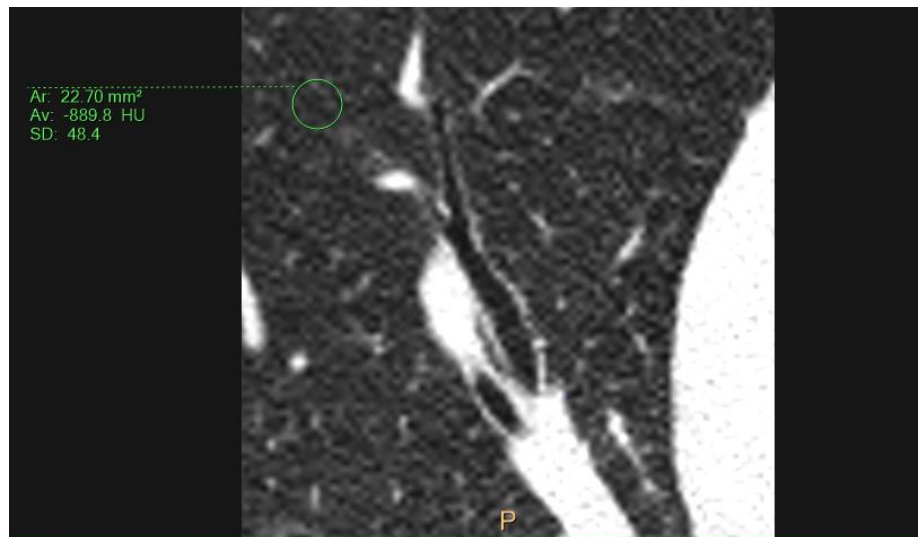


Human lung imaging

Lung CT (120 kVp, **105 mAs**, BMI 25)



Lung SPCCT (120 kVp, **62 mAs**, BMI 25)



B64 acquisition

120 kVp, 105 mAs

FOV 350 mm, matrix 512 mm

Slice thickness 0.80 mm

Filter detailed

SPCCT acquisition

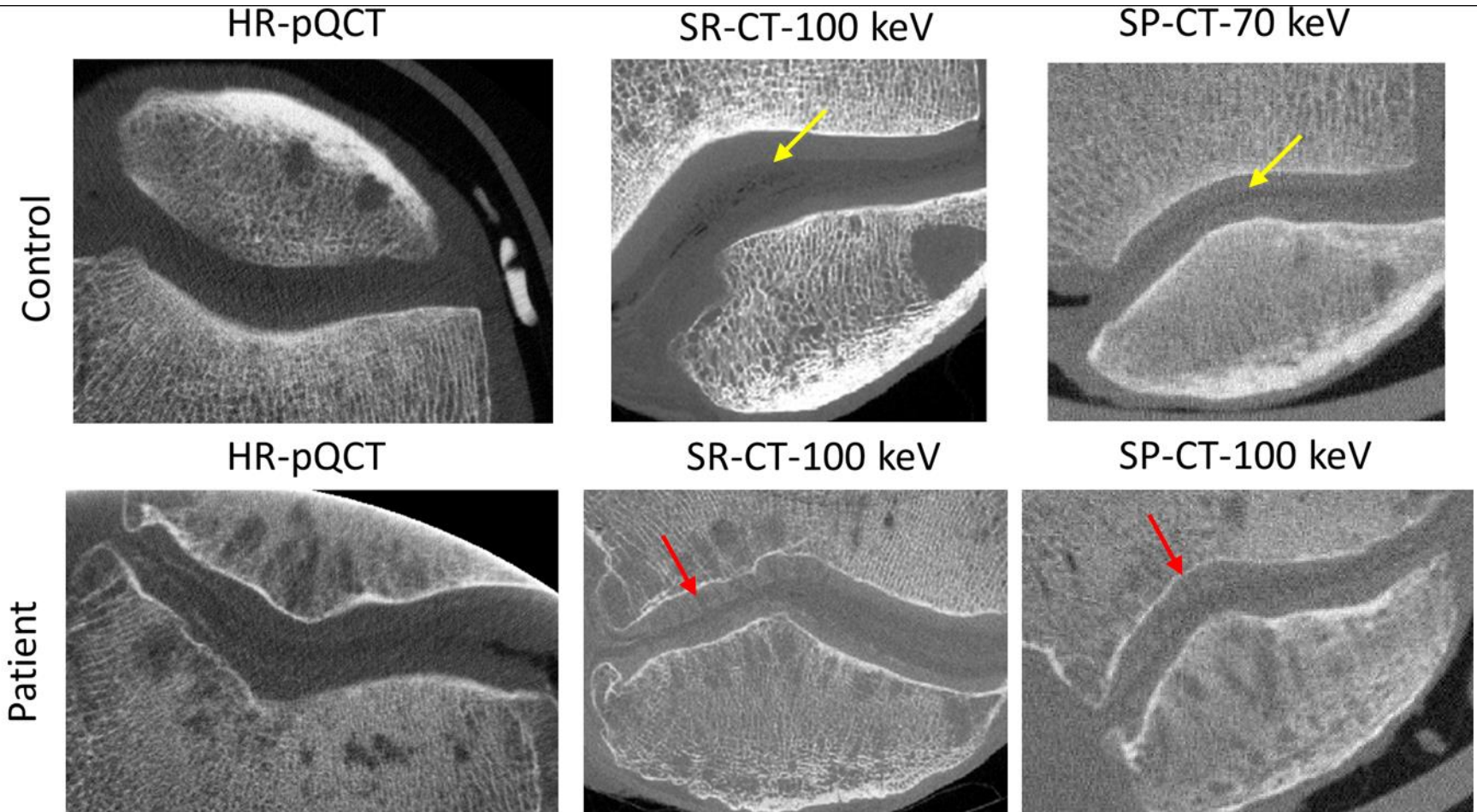
120 kVp, 62 mAs

FOV 350 mm, matrix 512 mm

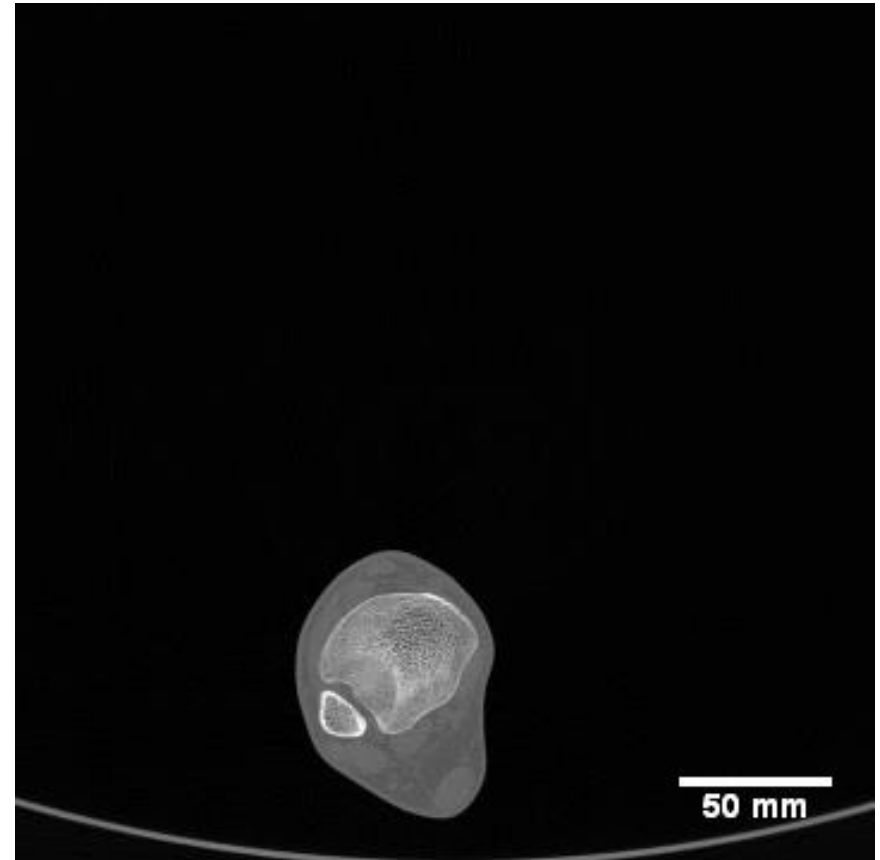
Slice thickness 0.75 mm

Filter detailed

Human knee imaging



Roentgen bone imaging



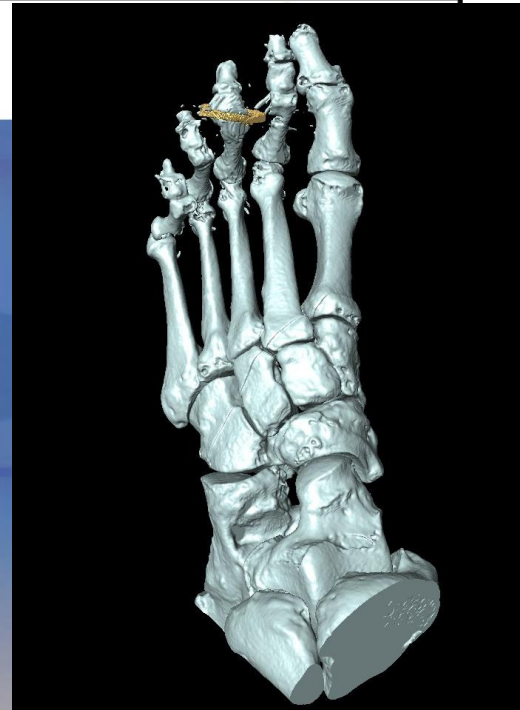


Creatis

CERMSP
imagerie du vivant



Hand mit Röntgen



Pied en SPCCT

Thank you for your attention



Aknowledgements

University Lyon1 Claude Bernard, Creatis Laboratory, CNRS UMR 5220, INSERM U1206 | Hospices Civils de Lyon, CERMEP, Centre d'imagerie du vivant | Philips, CT Clinical Science, Suresnes, France | Philips Research Laboratories, Hamburg, Germany | Philips, Global Advanced Technologies, CT, Haifa, Israel | BRACCO Imaging S.P.A | King's College, London | VOXCAN | Universita degli Studi di Torino | Erasmus University, Rotterdam | Cliniques Universitaires | Saint-Luc, Bruxelles | Lyon Ingenierie Projet | University of Pennsylvania | Technical University of Munich



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SPCCT
IMAGING ALL THE PHOTONS



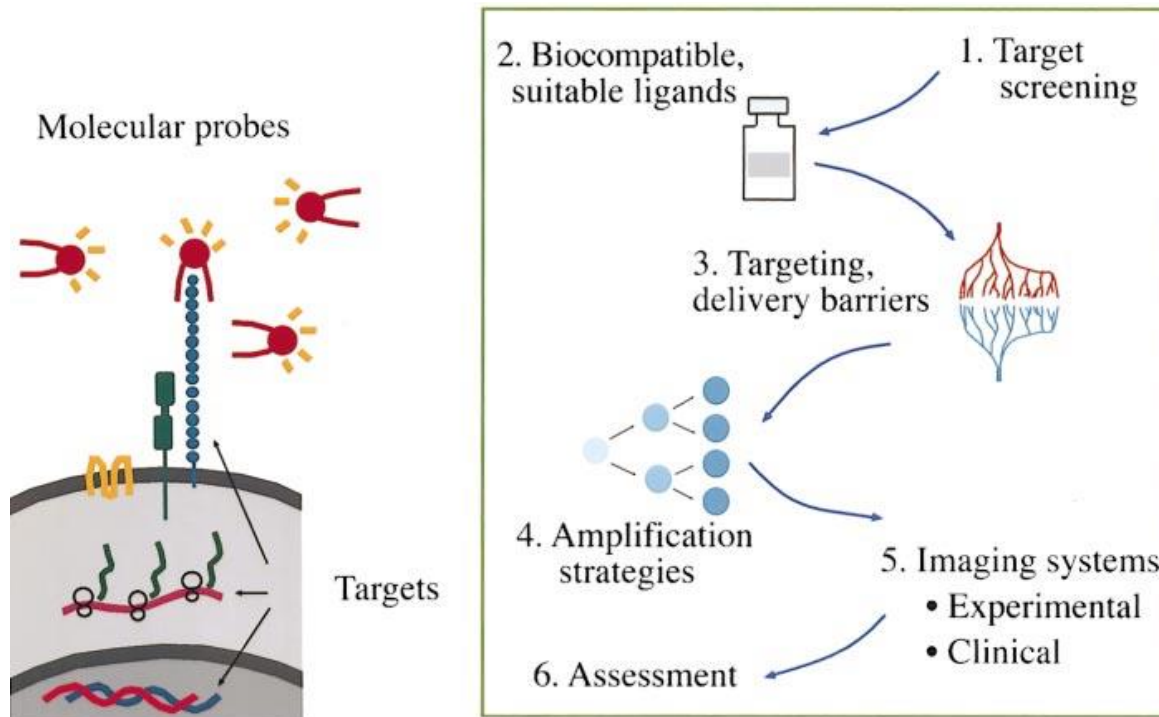
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Work remaining

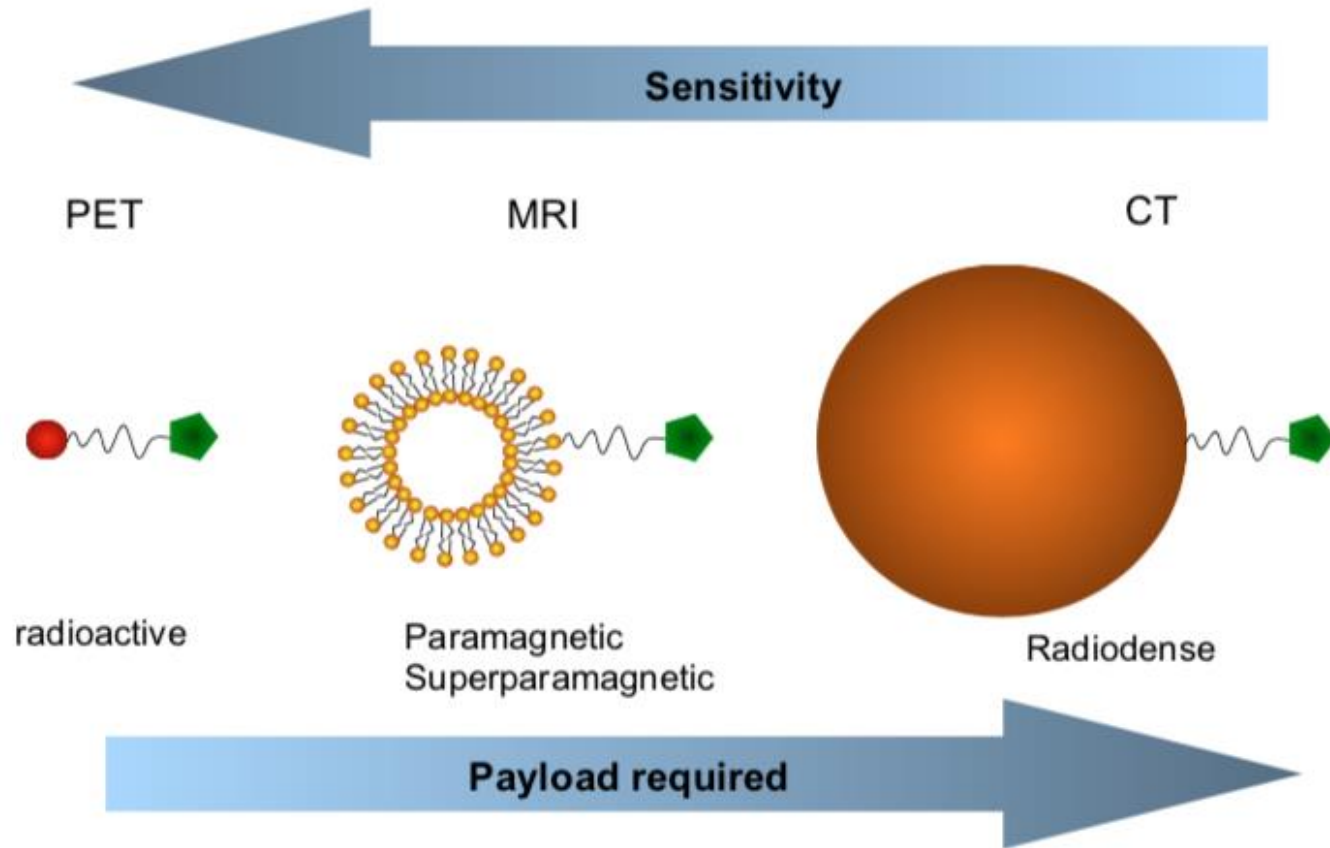
- 1) Quantify the gold concentrations per slices
- 2) Compare the gold concentrations to the area of macrophages within the plaques

SPCCT for molecular imaging



Need for **macrophage imaging** with SPCCT

Imaging modality sensitivity to contrast



Need for **macrophage imaging** with SPCCT

Gold nanoparticles

- Gold nanoparticles
 - Characteristics:
 - capped with thiol-PEG-2000
 - mean hydrodynamic radius of 18 nm
 - concentration: 65 mg/ml of gold
- Strong CT contrast
- Good candidate for K-edge imaging
- Good candidate for the vascular system initially and for the mononuclear phagocyte system over time

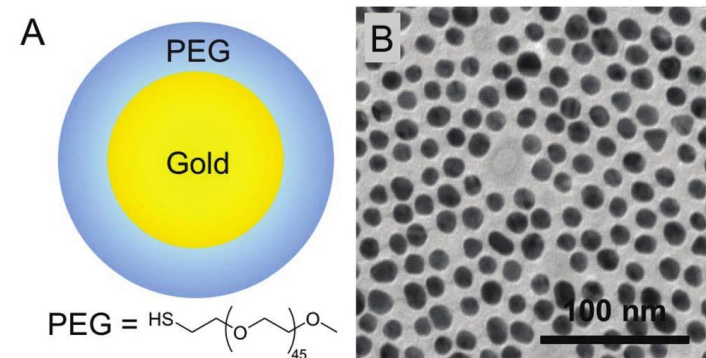
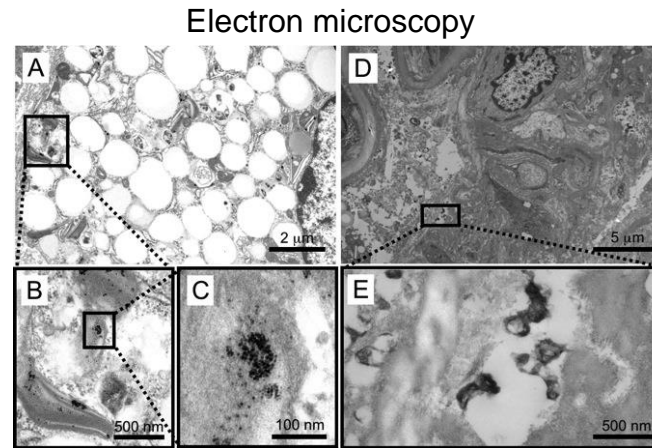
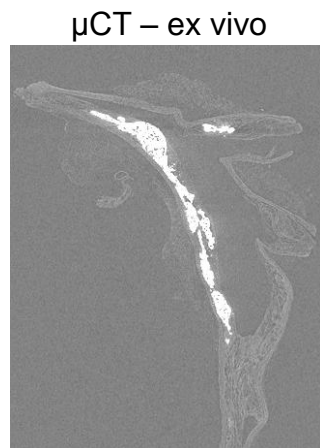
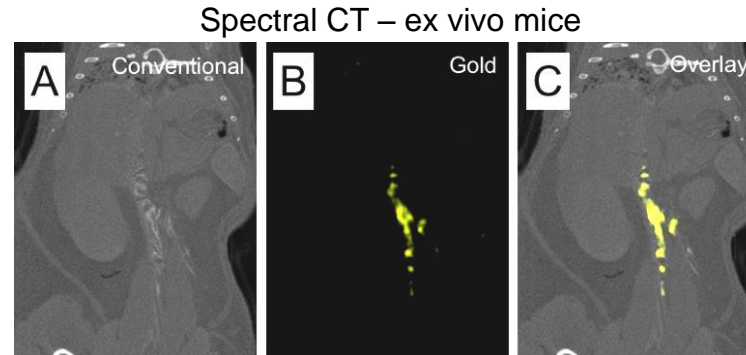
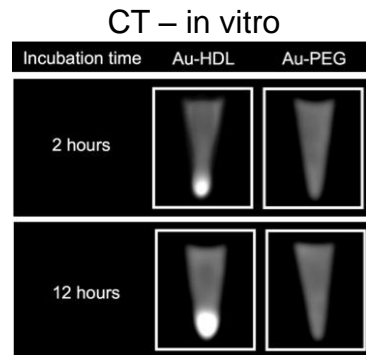


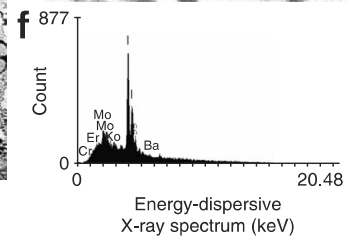
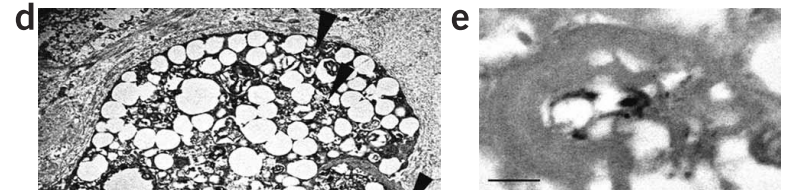
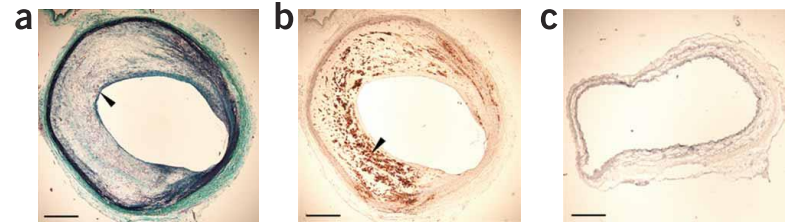
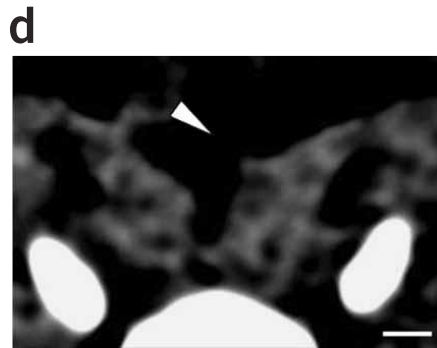
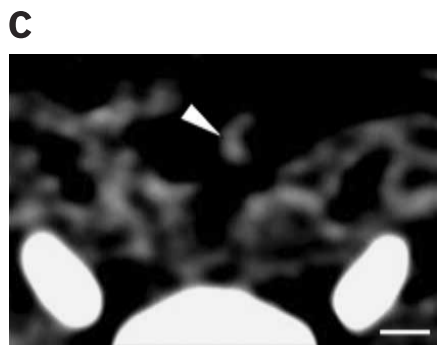
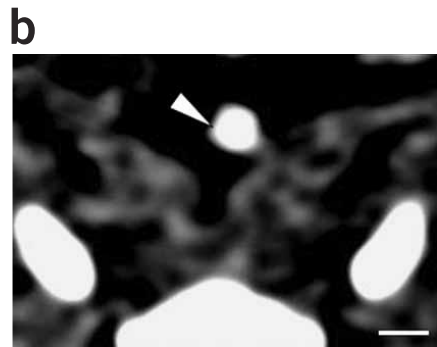
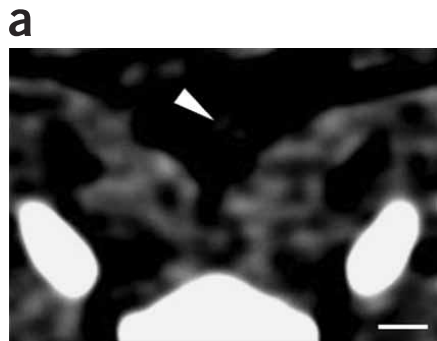
Fig. 1 (A) Schematic representation of the AuNP. (B) Transmission electron micrograph of the AuNP.

SPCCT for specific imaging

Feasibility for **molecular imaging** of the plaque components in an ex vivo model



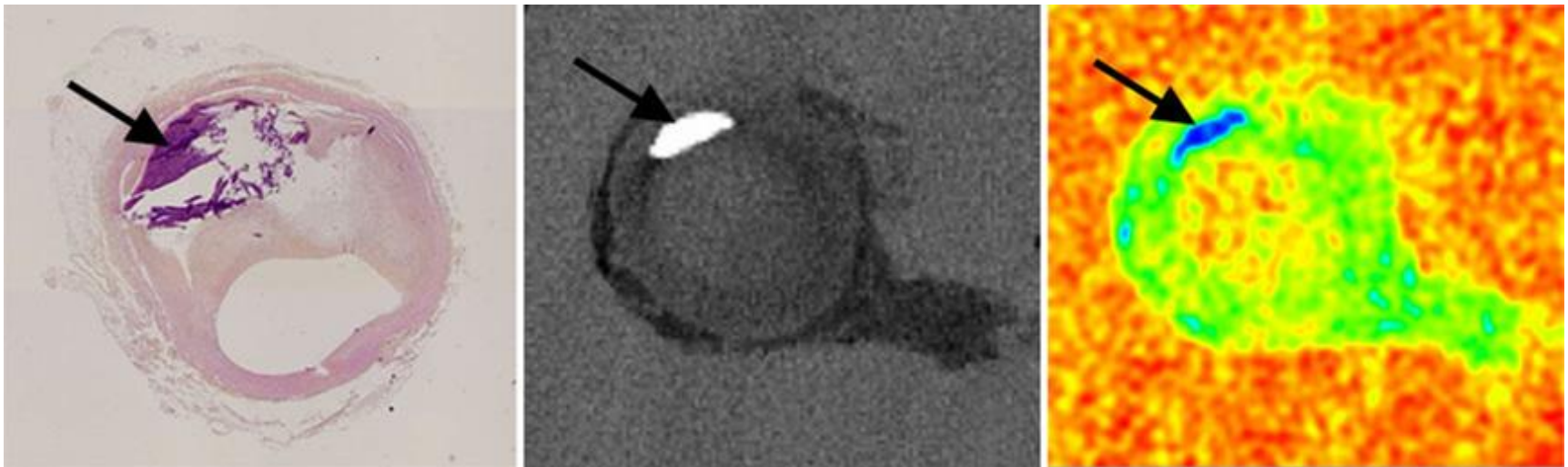
Need for a **macrophage** imaging



SPCCT for coronary imaging

High contrast resolution modality

- Potentiel for discrimination of the calcifications
- But still limited by the **characterization** of the plaque components



Need for **cellular imaging** with SPCCT

MicroCT for coronary imaging

High resolution modality

- Potentiel for delineation of the burden
- But still limited by the **characterization** of the plaque components



Need for **cellular imaging** with SPCCT