IMAGING AND UNDERSTANDING OF CARDIO-VASCULAR DISEASES

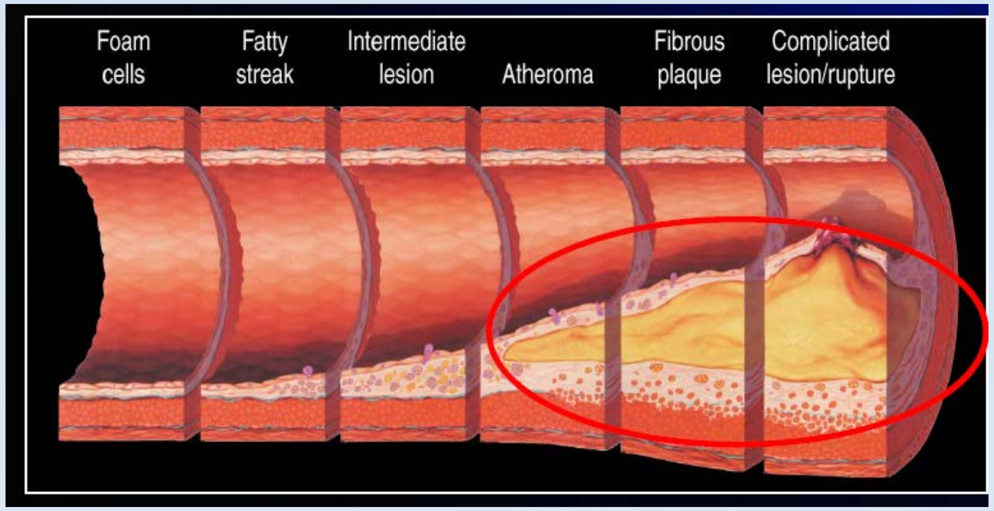
Imaging and understanding of cardio-vascular diseases

- Simulation, Modeling and Imaging to address clinical or physiopathological questions

- Cardio-vascular diseases :
  - Main source of mortality and morbidity in developed countries
  - Selection of "at-risk" patients for optimal prevention of CV acute events
  - New therapies:
    - Targeting the good phenomenon for the good patient
    - Treatments evaluation
  - Focus on cardiac and cerebral ischemia

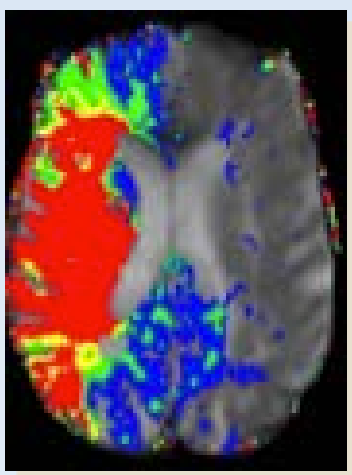
Plaque progression, rupture and thrombus

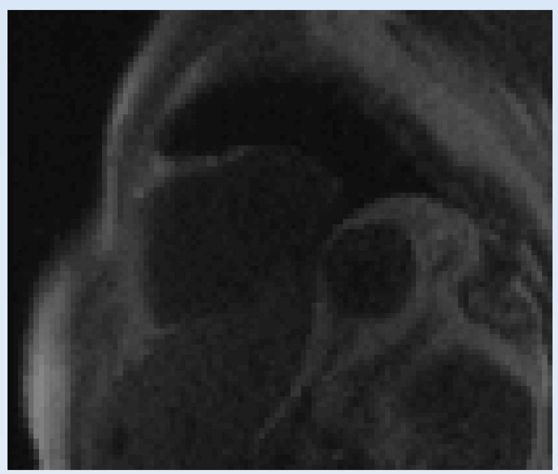
Main mechanisms



Inflammation
Lipid metabolism
Blood Flow (Wall Shear Stress)
Platelet activation - Coagulation

Ischemia, necrosis and reperfusion lesions





Anoxia - Stunning - Hibernation
Inflammation
Reperfusion lesions

Healing and sequels

Tissue remodeling
Fibrosis

Imaging and understanding of cardio-vascular diseases

- Global comprehensive approach of CV disease by multi-modal (PET, CT, MR, US, X-ray), hybrid and multi-scale imaging (clinical and preclinical models):

Imaging	**Main challenges**
Morphology	Small varying caliber and geometry of vessels (->coronary arteries) Tissue characterization: - Heterogeneous plaque components - Complex cardiac fibers architecture Thrombus formation: Simulations
Motion	Cardiac motion assessment and quantification Contrast uptake and quantification Sources of artifacts: cardiac and respiratory motion
Inflammation	Unspecific to specific contrast agents
Hemodynamic	Limitations in in-vivo measurement Flow simulations

Imaging and understanding of cardio-vascular diseases

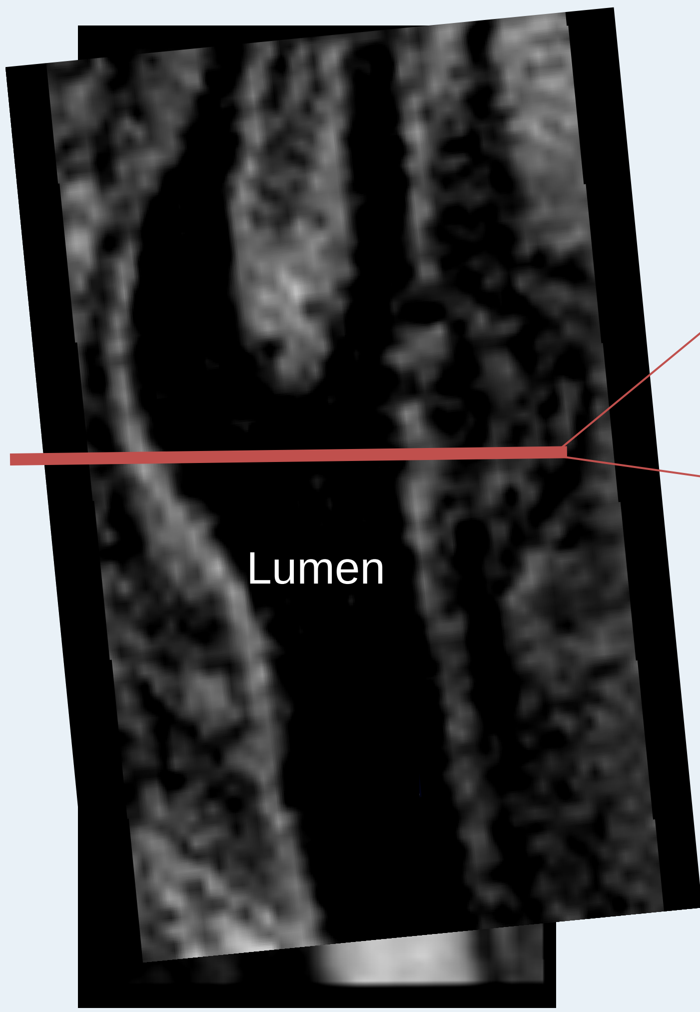
- **Multi-teams approach:**
  - Multimodal image acquisition: Teams 1, 3, 5 and 6
  - Image reconstruction and post-processing: Teams 1, 2, 4, 5 and 6
  - Simulations: Teams 1 and 2
- **Following presentation:**
  - Monica Sigovan: Main challenge for clinical evaluation of vascular disease: Early and accurate risk assessment for the occurrence of clinical manifestations
  - Marlène Wiart: Stroke and inflammation on preclinical models
  - Patrick Clarysse: Cardiac imaging

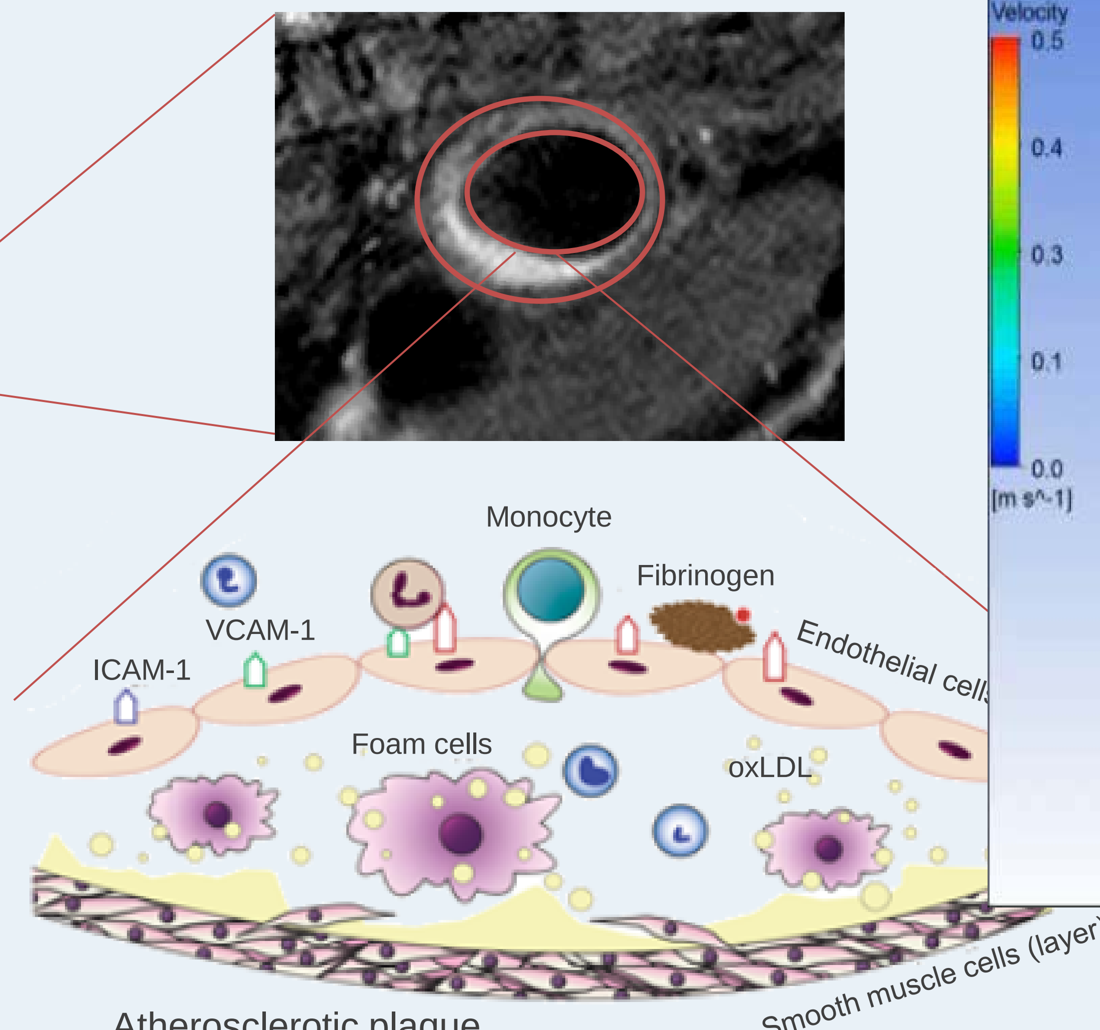
Vascular Imaging implies:

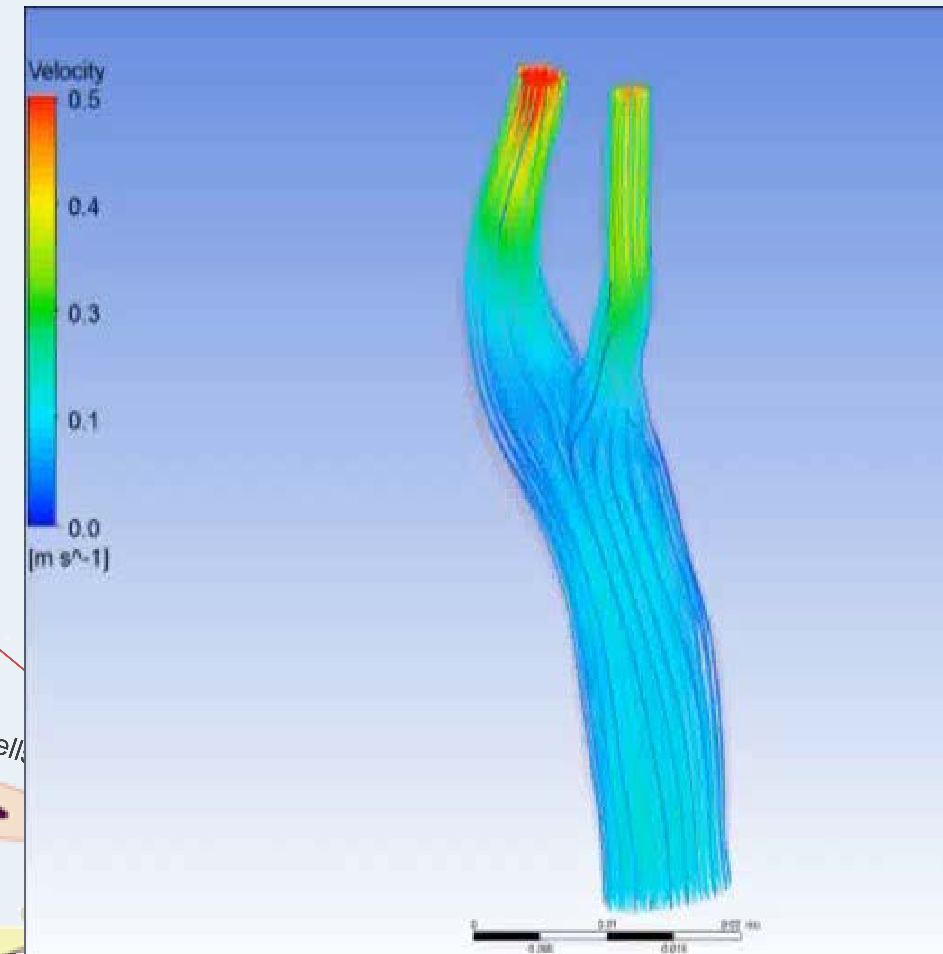
A **vessel lumen**
varying caliber and geometry

A **vessel wall**
- relatively thin:
aorta 1 - 4 mm, coronaries >1mm
- heterogeneous composition

Types of Motion
1. **Blood flow**
2. **Wall motion**







CFD simulation
Human carotid artery

MORPHOLOGY

PHYSIOLOGY

HEMODYNAMICS

Main challenge for clinical evaluation of vascular disease:

- **Early and accurate evaluation of the risk of occurrence of clinical events (stroke, myocardial infarction…)**

Research objectives of the Vascular Imaging Team:

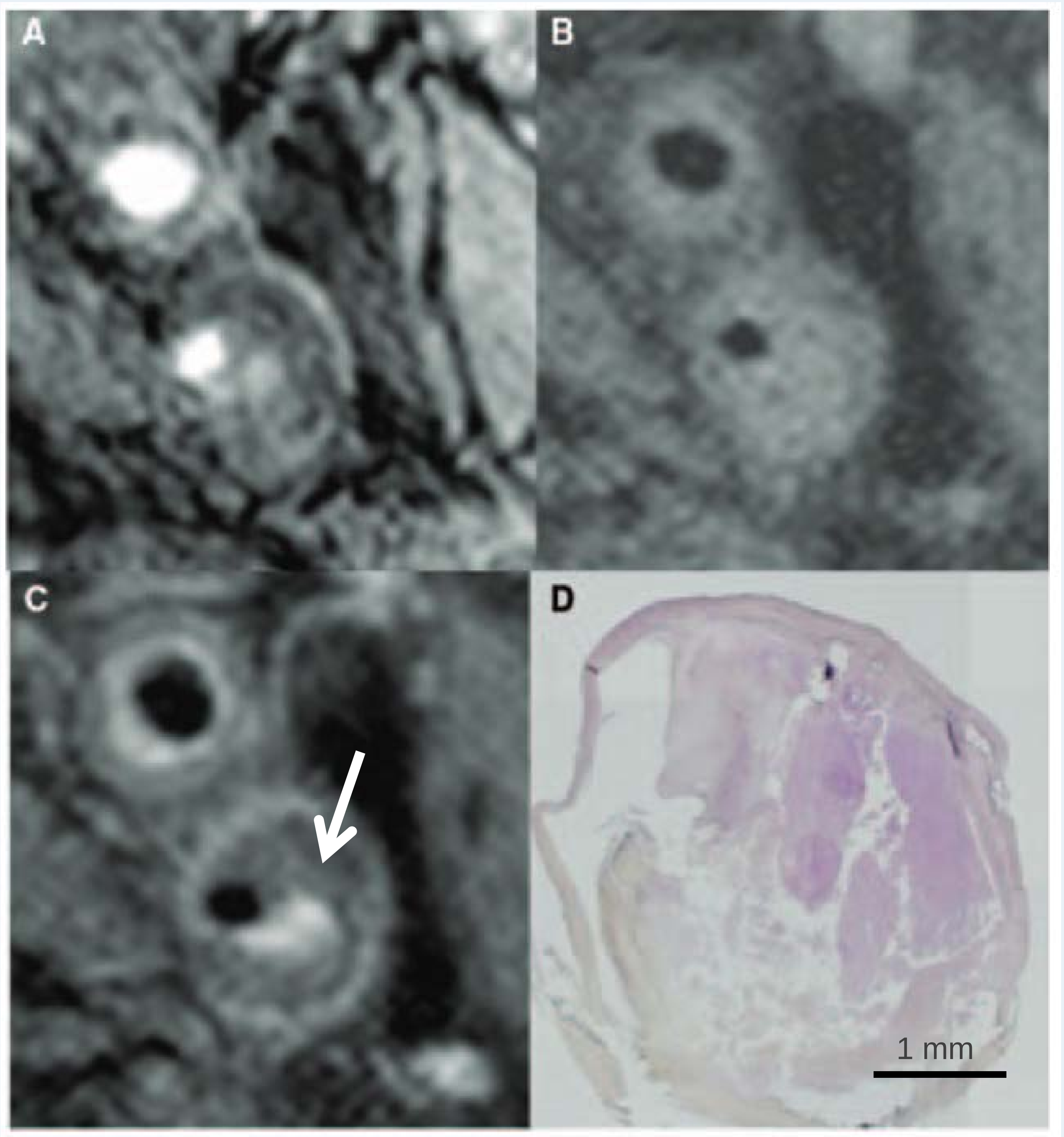
- *Short-term*:
  - Improve our understanding of **vascular pathologies** by the joint study of **morphology**, **physiology** and **hemodynamics**
- *Long-term*:
  - Propose novel combined imaging and post-processing methods enabling a

"one-stop shop" multi-modality imaging for risk evaluation of vascular diseases

- **Clinical setting:**

Gd-enhancement

Low specificity



[A Millon, L Boussel et al, Stroke 2012]

Imaging Vessel Physiology

- **Pre-clinical setting:**

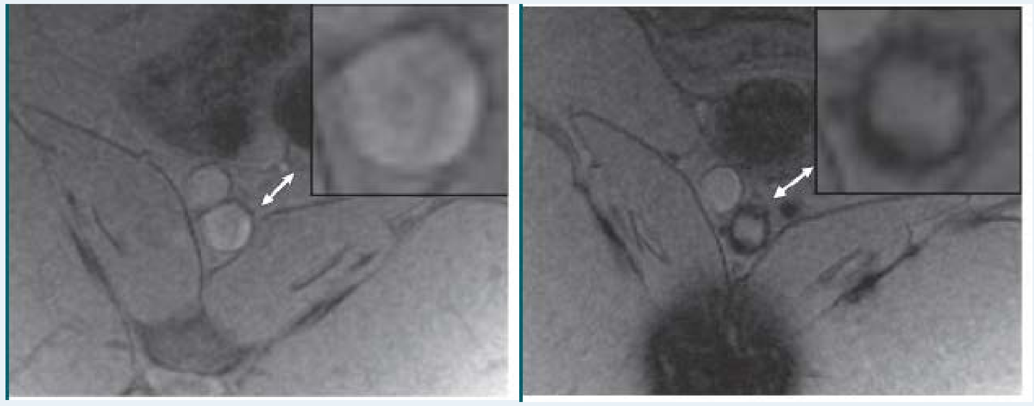
USPIO-enhancement

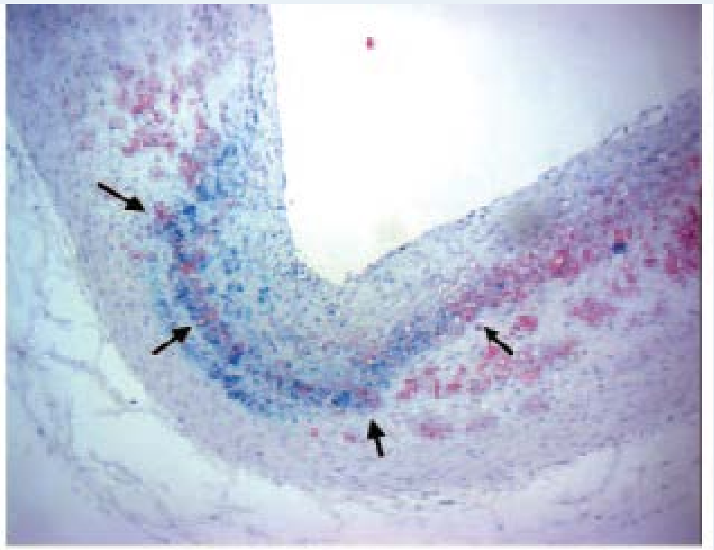
Inflammatory regions

72h Post USPIO (Guerbet)

axial T2*-w GRE

pre-USPIO 72h post-USPIO





Histology (Perls blue)

Rabbit model / Abdominal Aorta

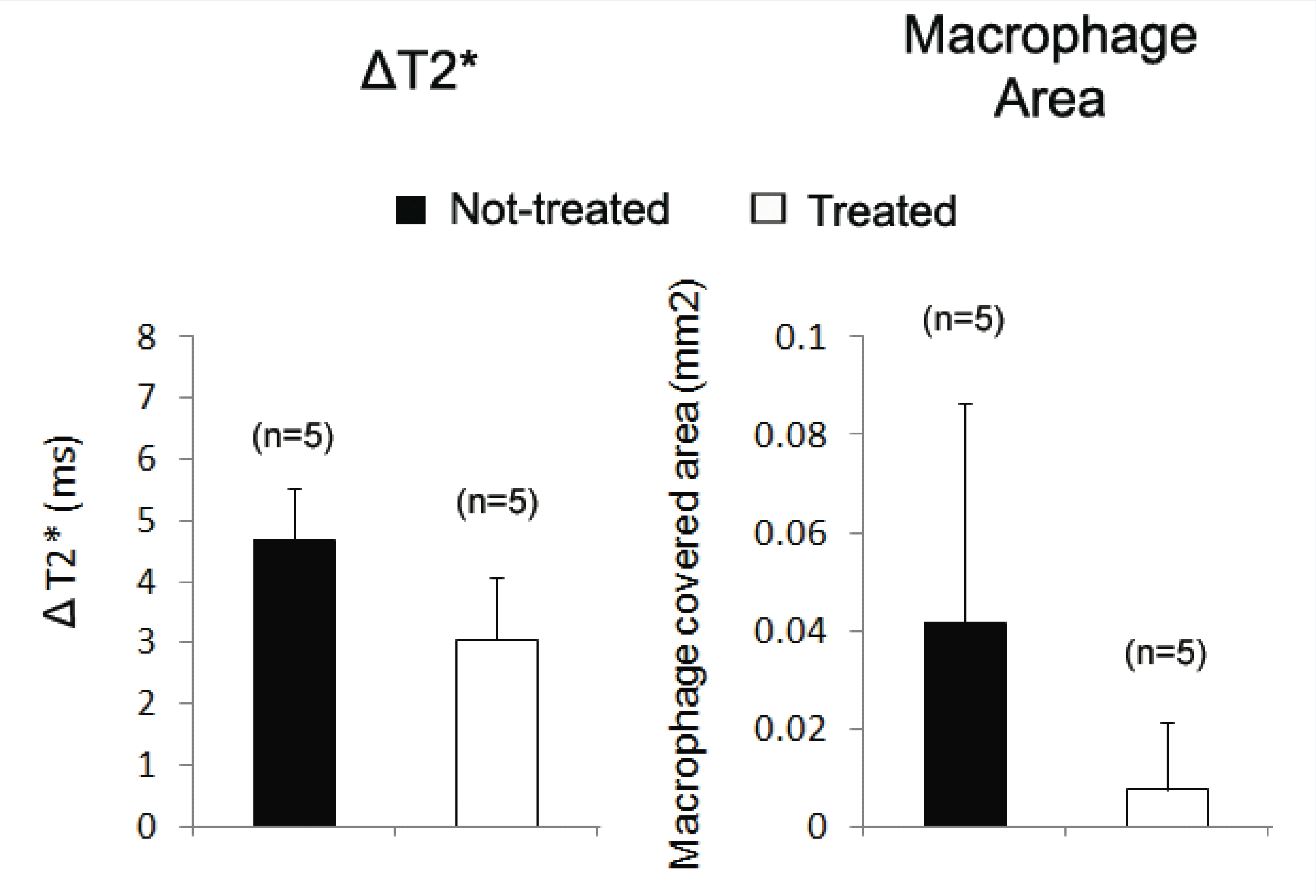
[M Sigovan, L Boussel et al, Radiology 2009]

- **Pre-clinical setting:**

USPIO-enhancement

Treatment response

□ **Irbesartan* treatment**



Mouse model (ApoE -/-) / Thoracic Aorta

[Sigovan et al, Investigative Radiology 2010&2012]

* Irbesartan – blocks monocyte production of inflammatory markers

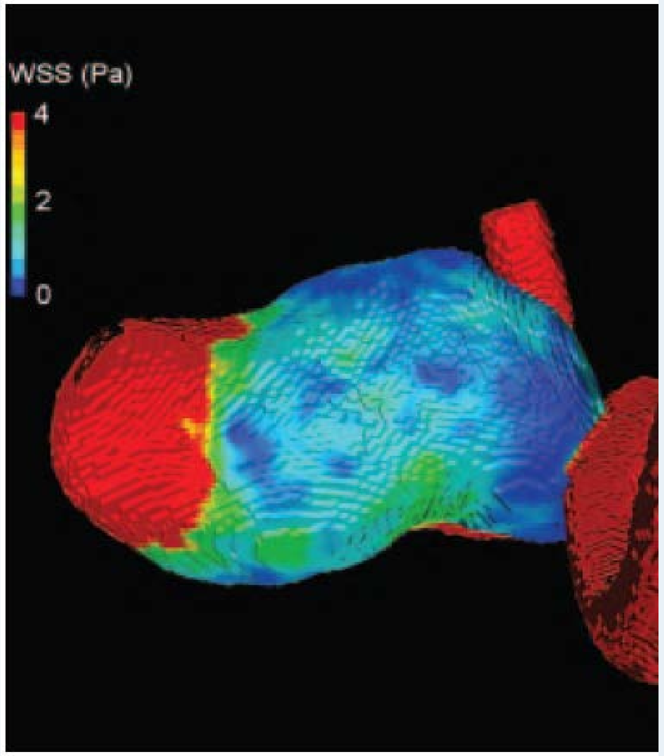
- **Indirect flow evaluation**

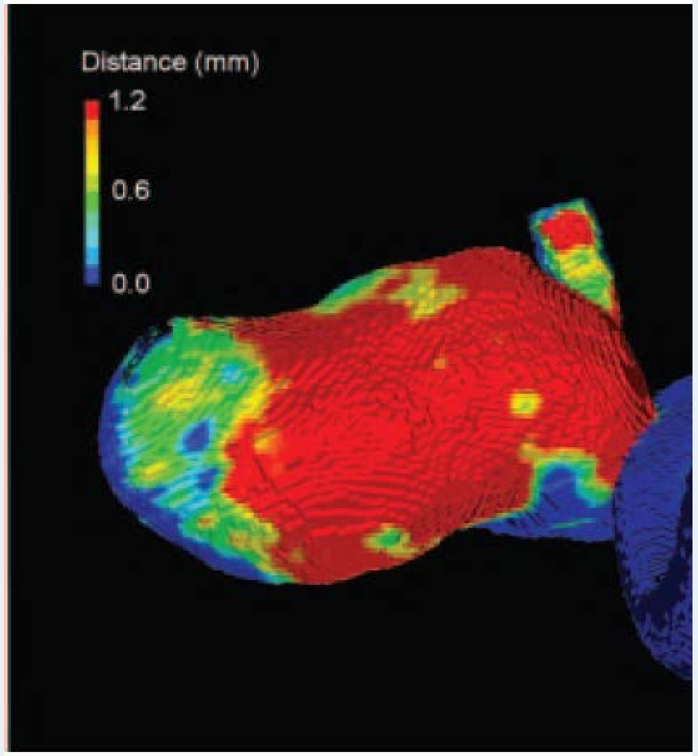
CFD simulations

Patient specific geometries

WSS map

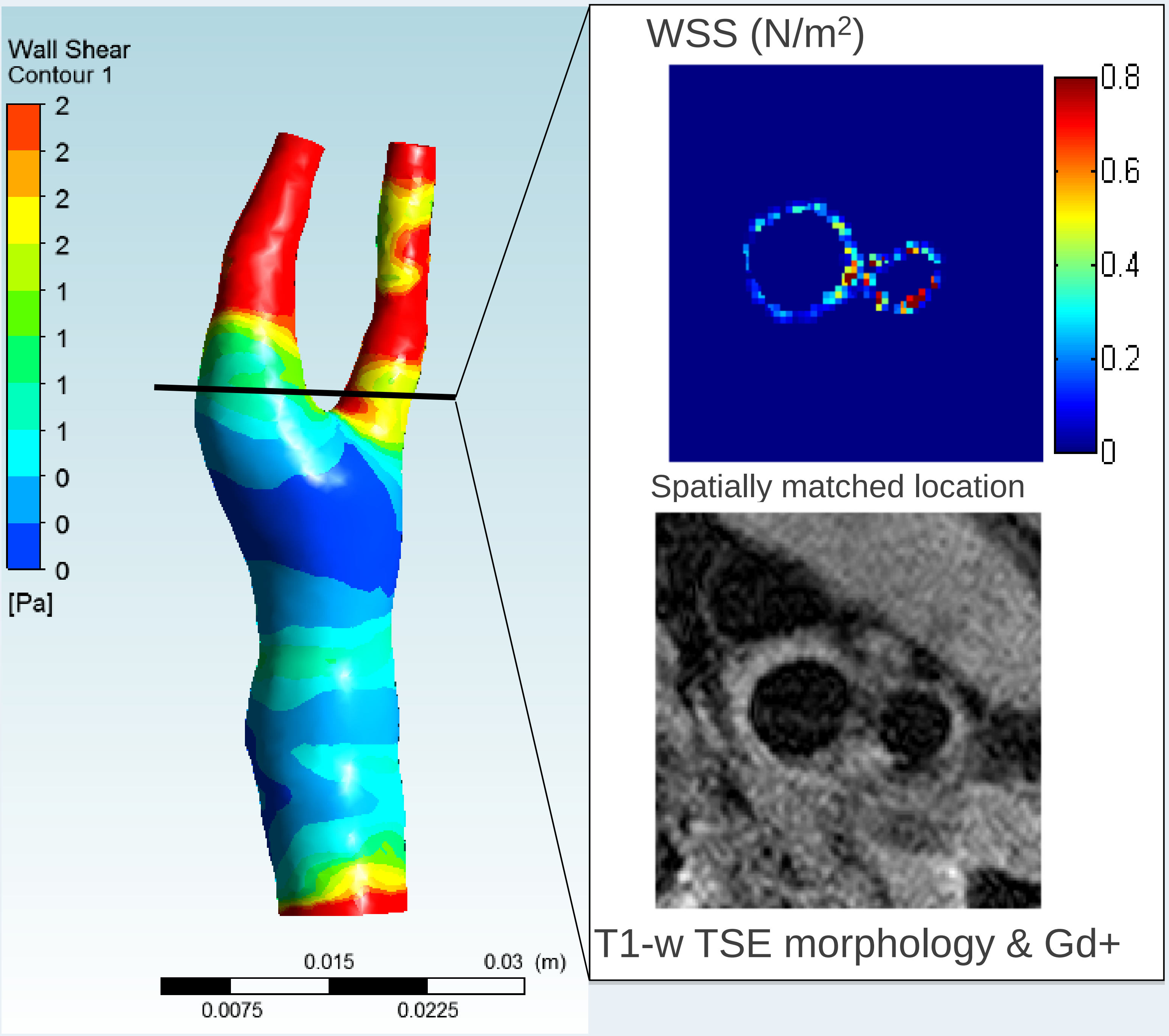
Aneurysm Growth map





[L Boussel et al, Stroke 2008]

Perspective : Simultaneous Analysis



- **Morphology & Physiology**

+

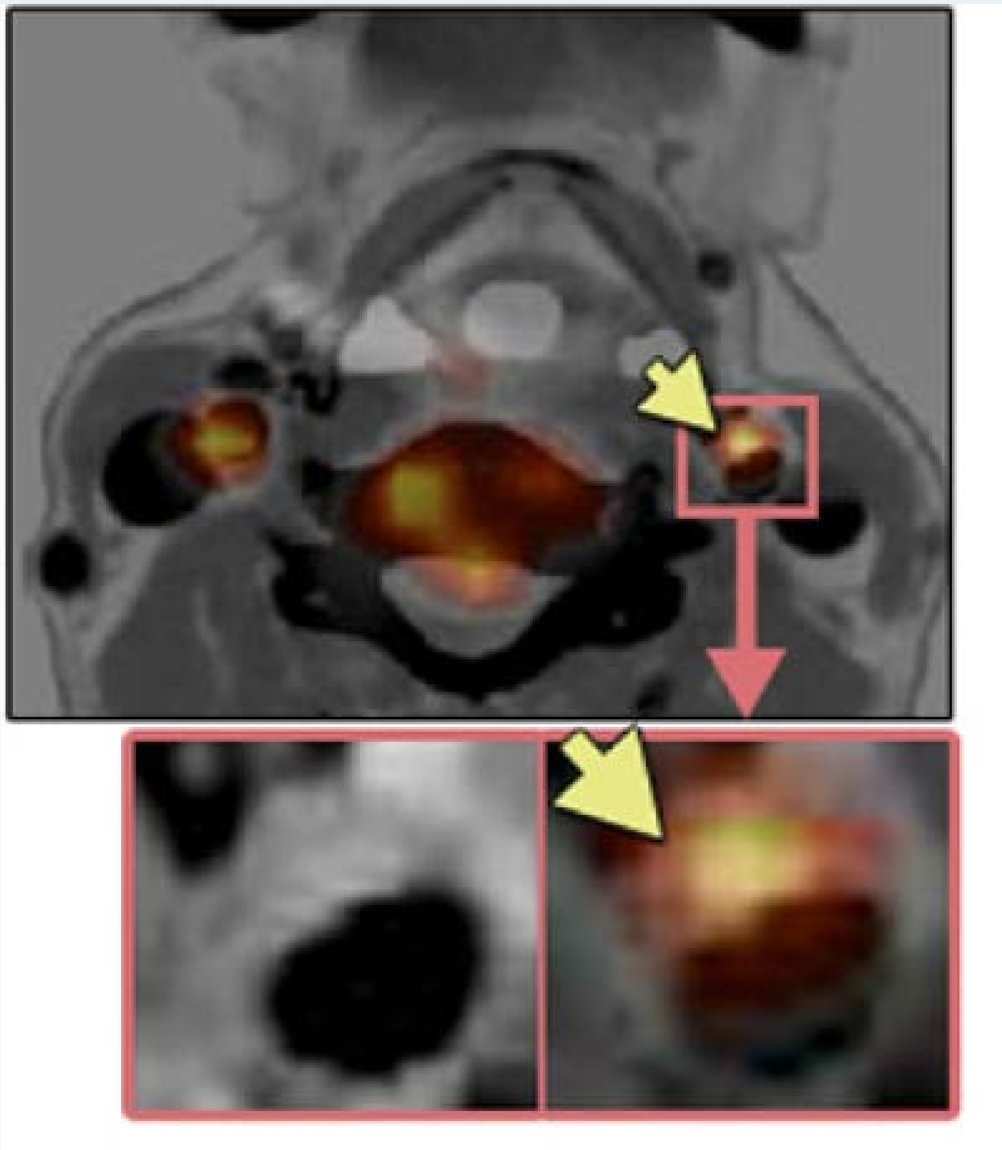
- **Hemodynamics**
  - Direct measurement MRI
  - CFD simulations (Team 1)

+

- **Wall motion**
  - US Team 3
    - o 2D radial and longitudinal deformation – carotid wall
  - 4D imaging (CT / MRI)
    - o post processing to estimate deformation (Team 1)

Perspective : Absolut contrast agent quantification

PET/CT -> Absolut quantification



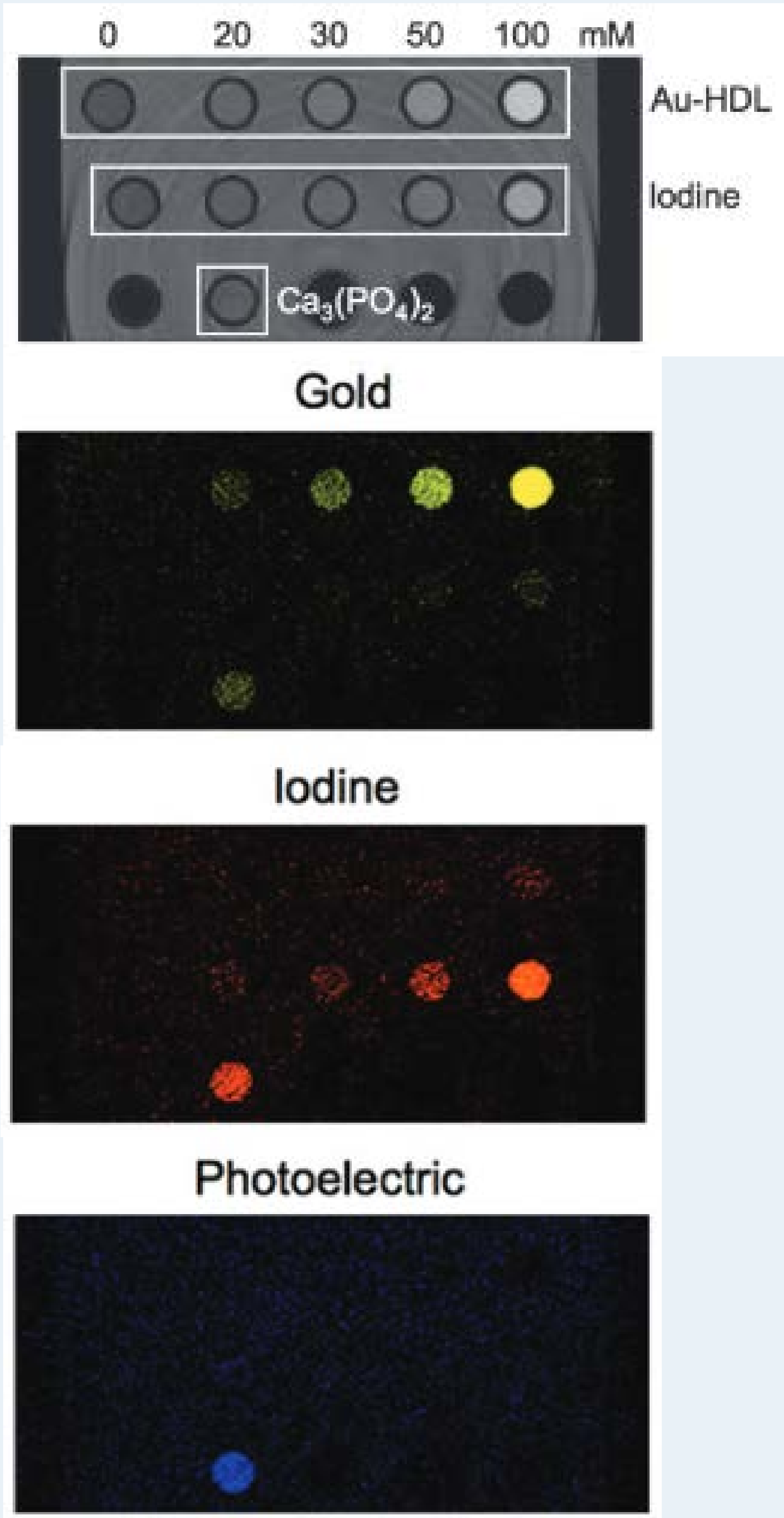
^{18}FDG accumulation in carotid arteries

[Mizoguchi et al, JACC2011]

PET/MRI
Hybrid Imaging
Quantitative CA uptake
+ Flow Imaging

Equipe x LiLi

Perspective : Spatial resolution & Specificity



[Cormode et al, Radiology 2010]

Tissue characterization/ Novel contrast agents

1. X-ray image reconstruction

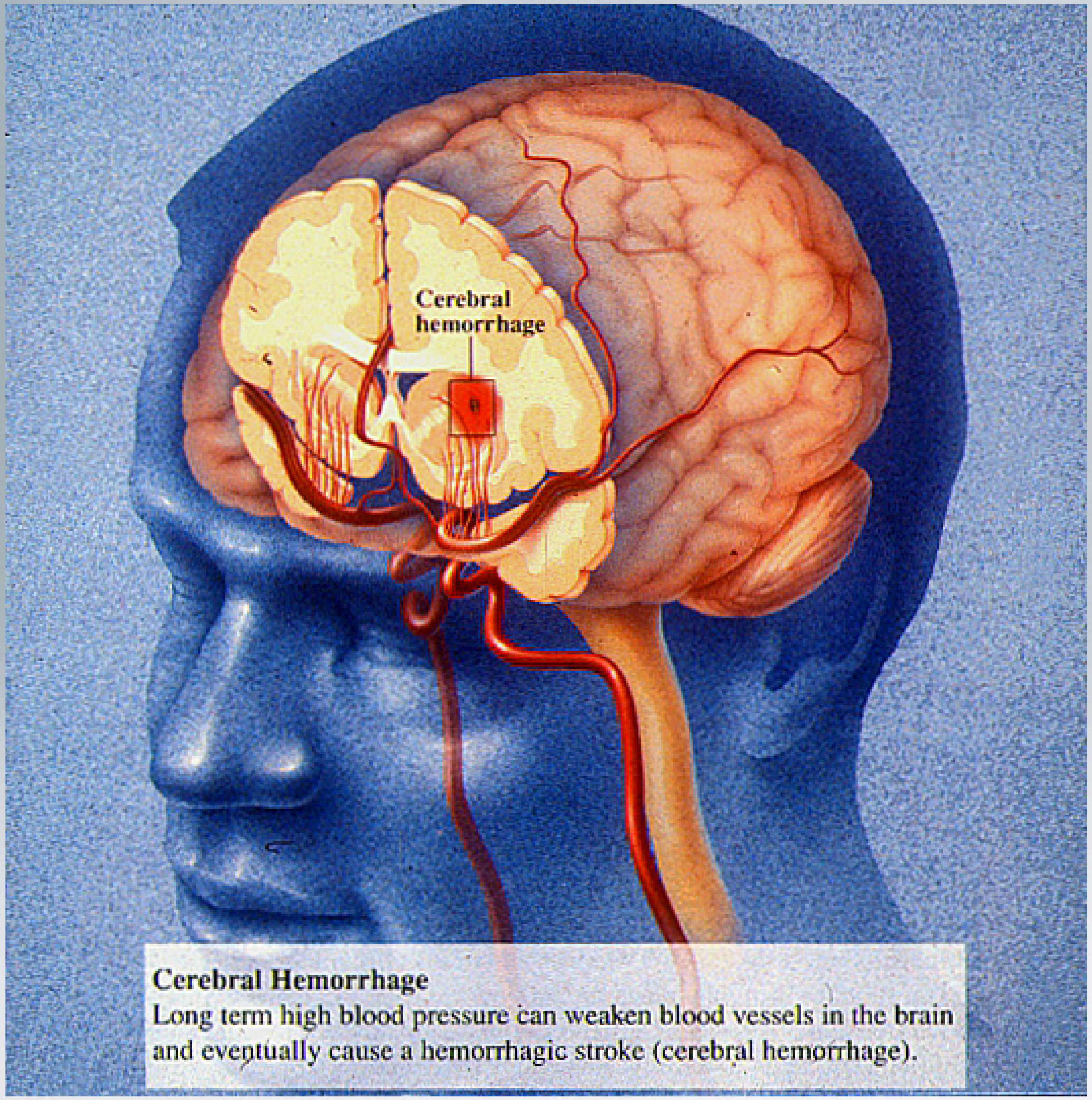
Creatis, Team 4 & ESRF – Prof. F. Peyrin

2. Contrast agent developement

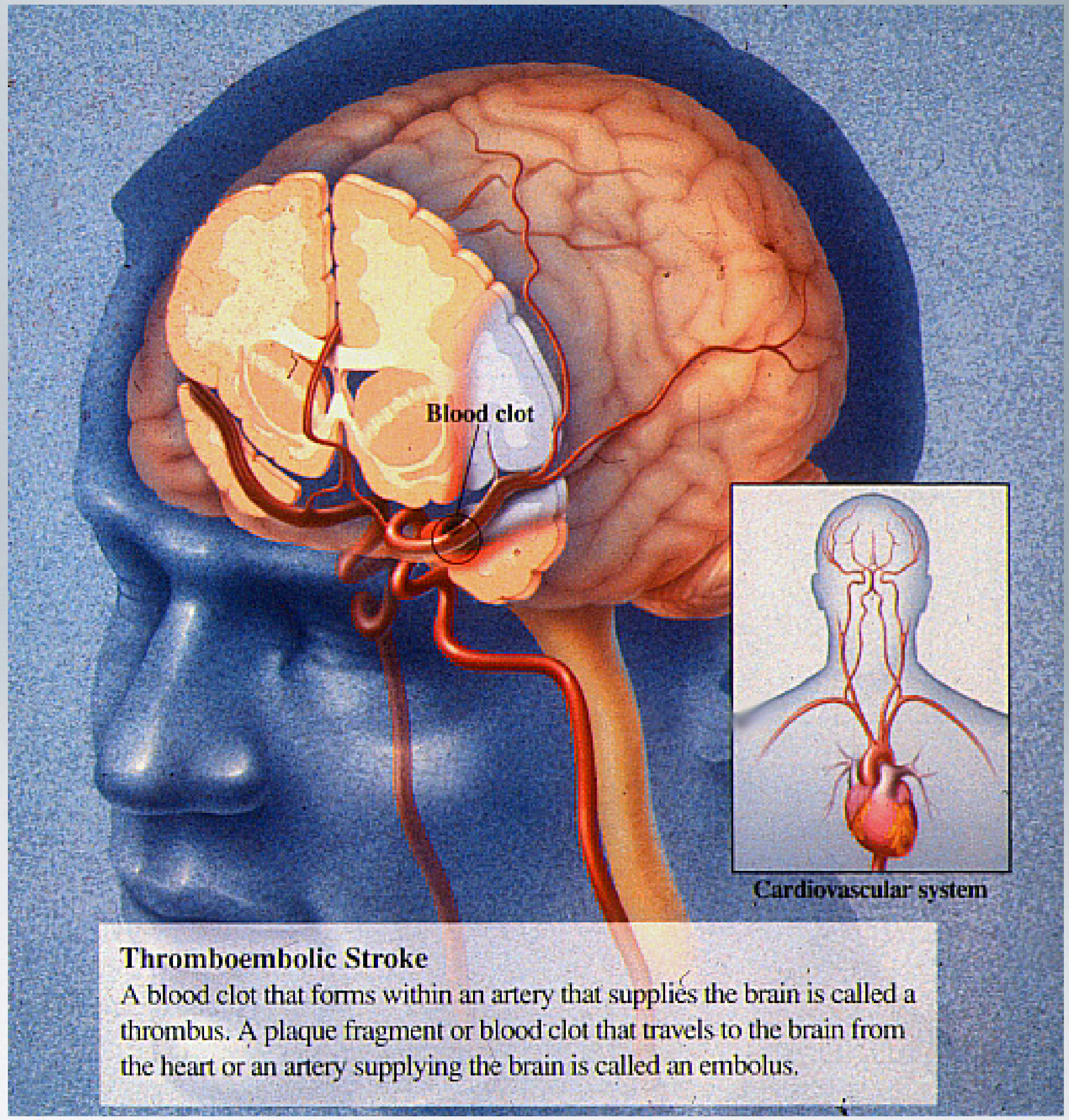
LAGEP Laboratory UMR CNRS 5007

Stroke

Hemorrhagic 20%



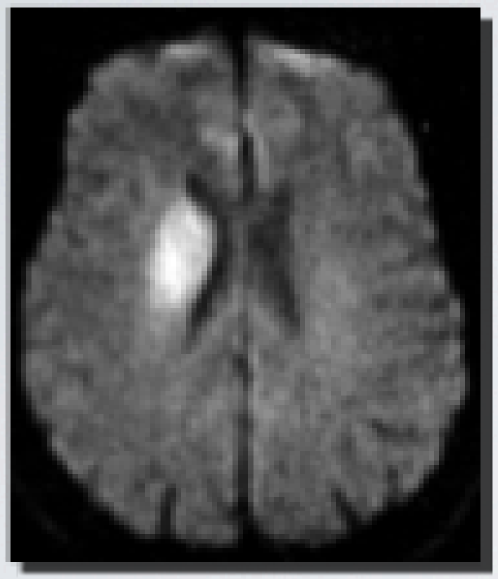
Ischemic 80%



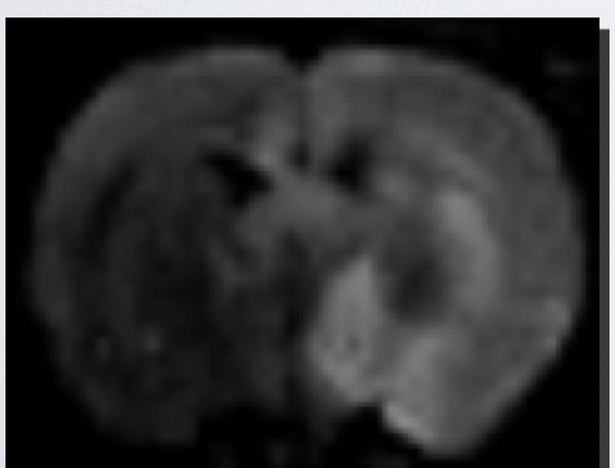
- ✓ **Third leading cause of death in industrialized countries**
- ✓ **Leading cause of significant disability**

MRI of cerebral ischemia

Diffusion-weighted imaging (DWI)



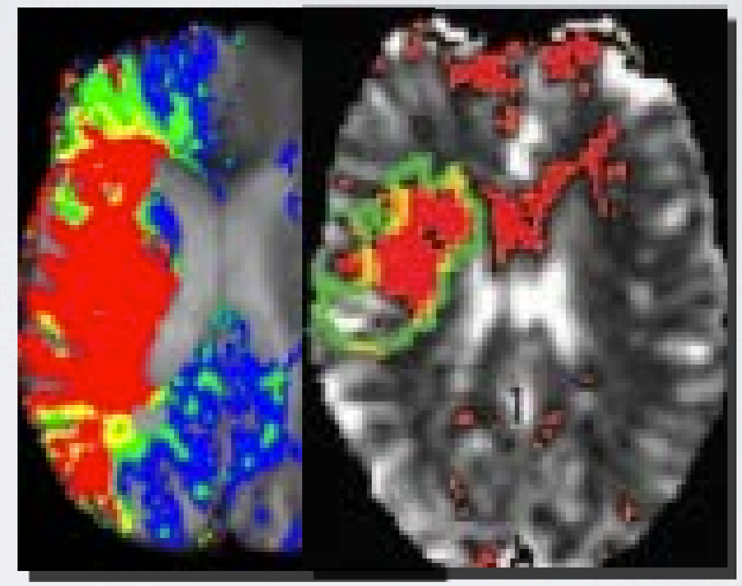
Necrosis



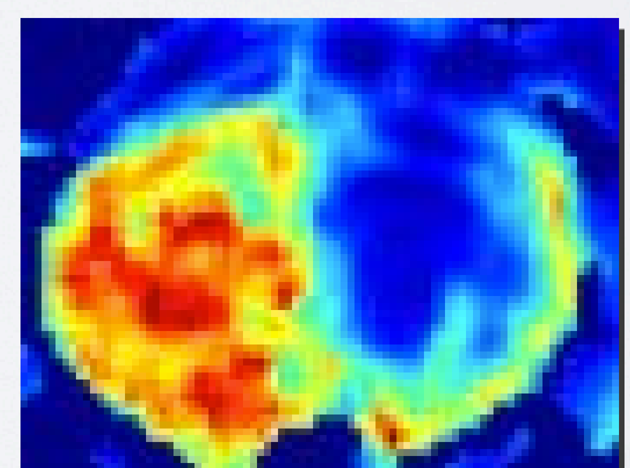
T2*-weighted imaging

Hematoma

Perfusion-weighted imaging (PWI)

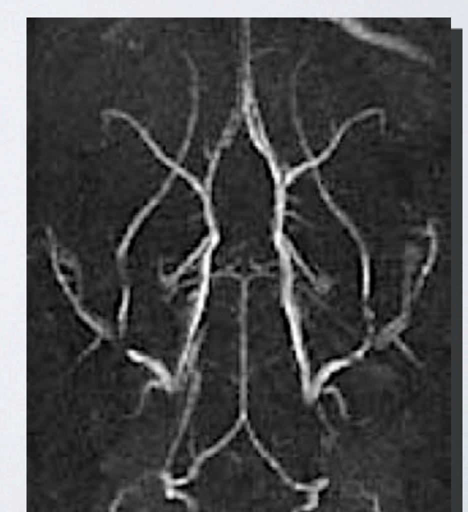


Tissue-at-risk



MR Angiography

Occlusion site



Aim: To image post-ischemic neuro-inflammation

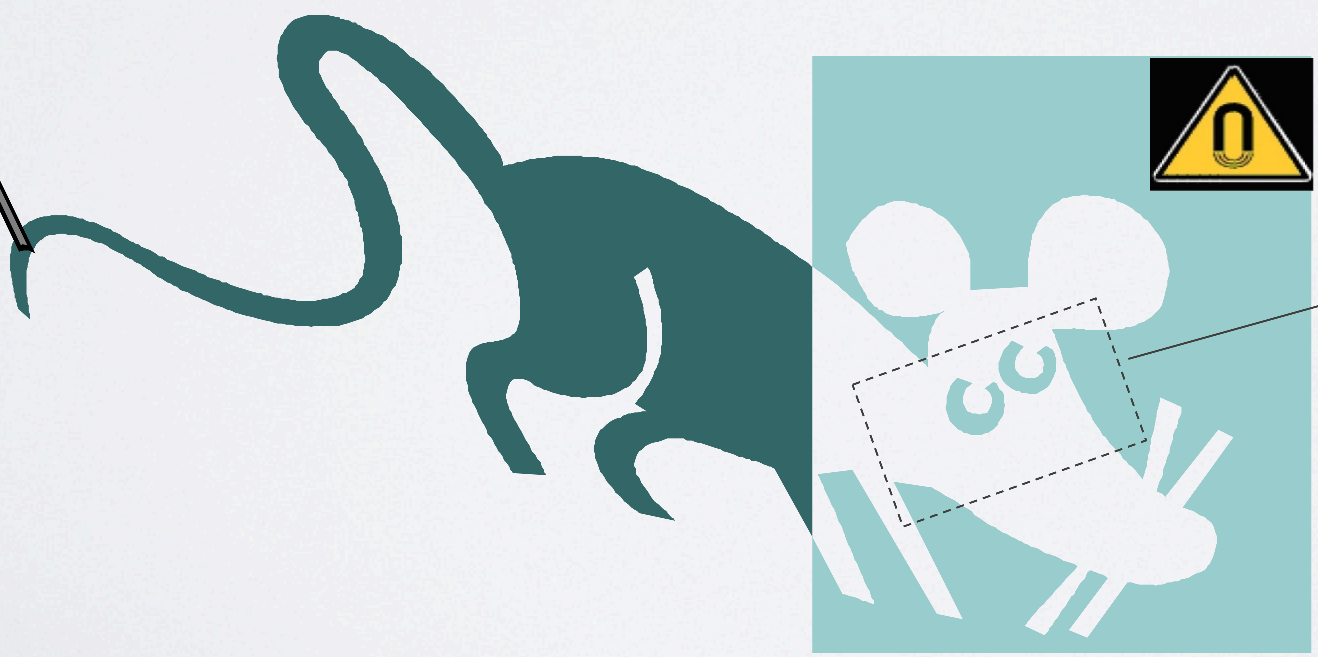
- ✓ Better understanding of **ischemic stroke physiopathology**
- ✓ **Evaluation of new treatments** for ischemic stroke patients

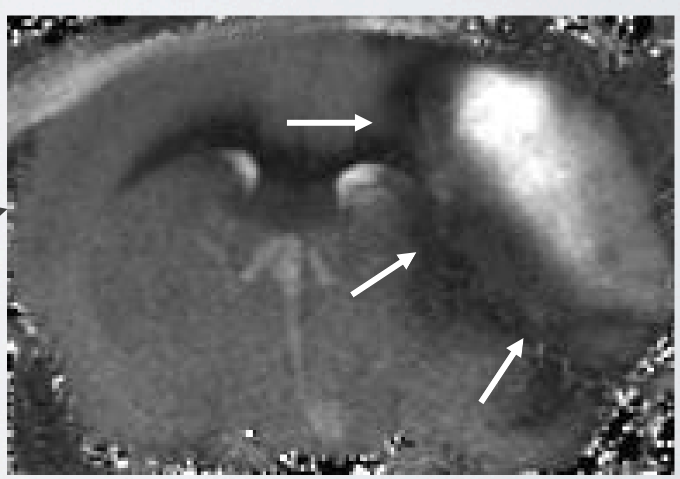
Principle of USPIO-enhanced MRI

Intravenous injection of ultrasmall superparamagnetic **particles of iron oxide (USPIO)**

In vivo **phagocytosis of USPIO by macrophages**

MRI detection at the lesion site





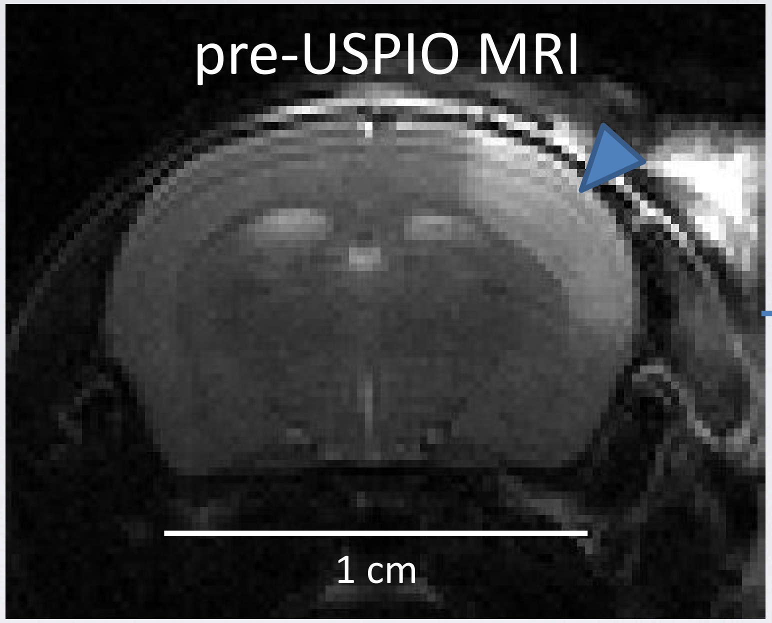
USPIOs as biomarkers of inflammation in stroke

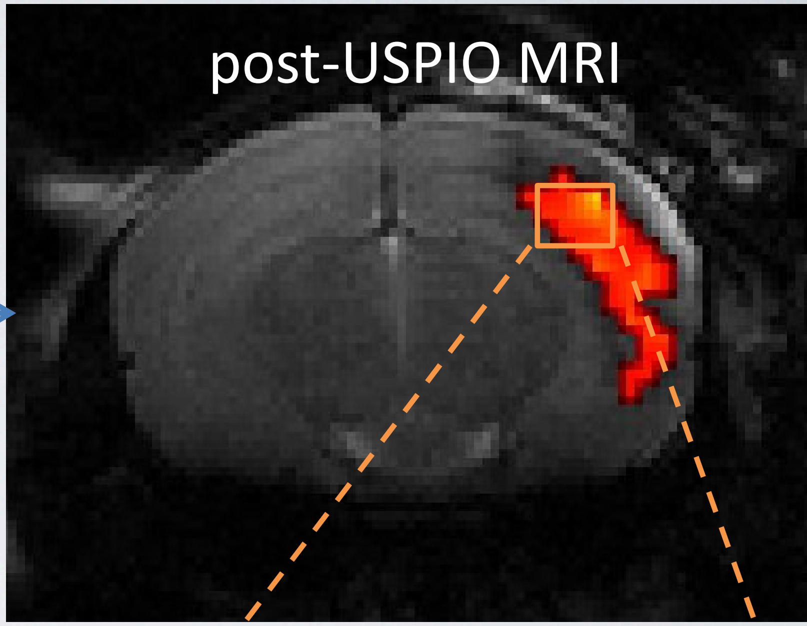
☺ Longitudinal study
Wiart et al., Stroke 2007

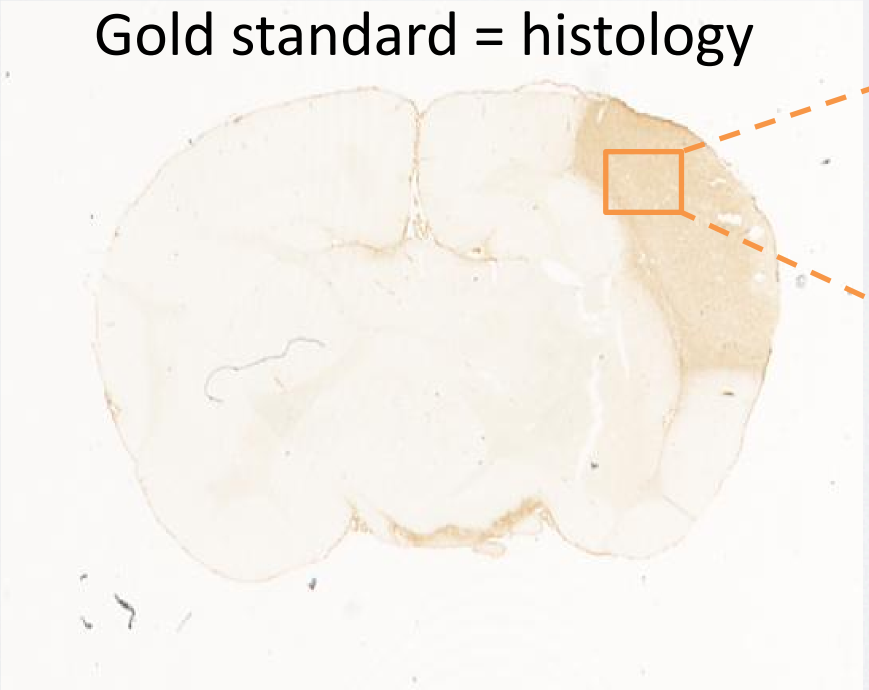
☺ Cellular imaging
Desestret et al, Stroke 2009

☺ Treatment monitoring
Marinescu et al, Eur Radiol 2013

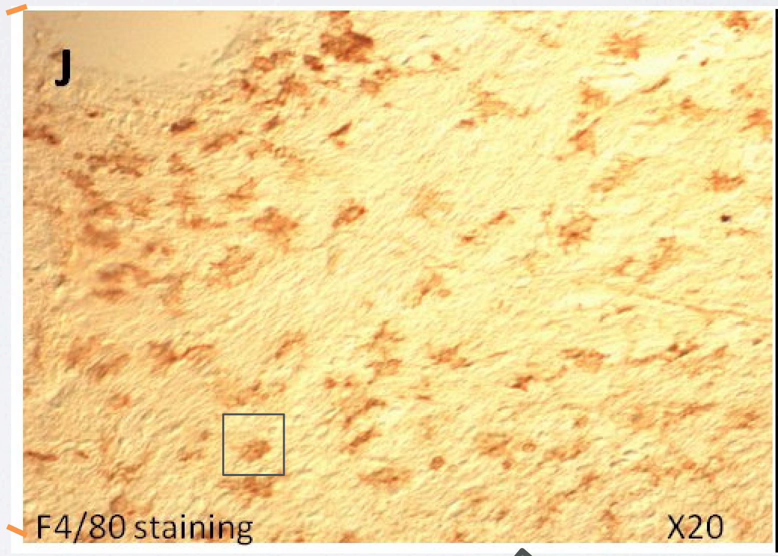
☺ Clinical translation
Nighoghossian et al, Stroke 2007 ; Cho et al, Cerebrovasc Dis 2008





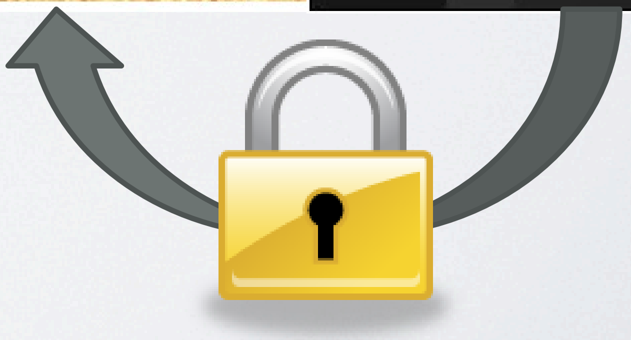


☹ Slicing, staining, distorsions



156 µm

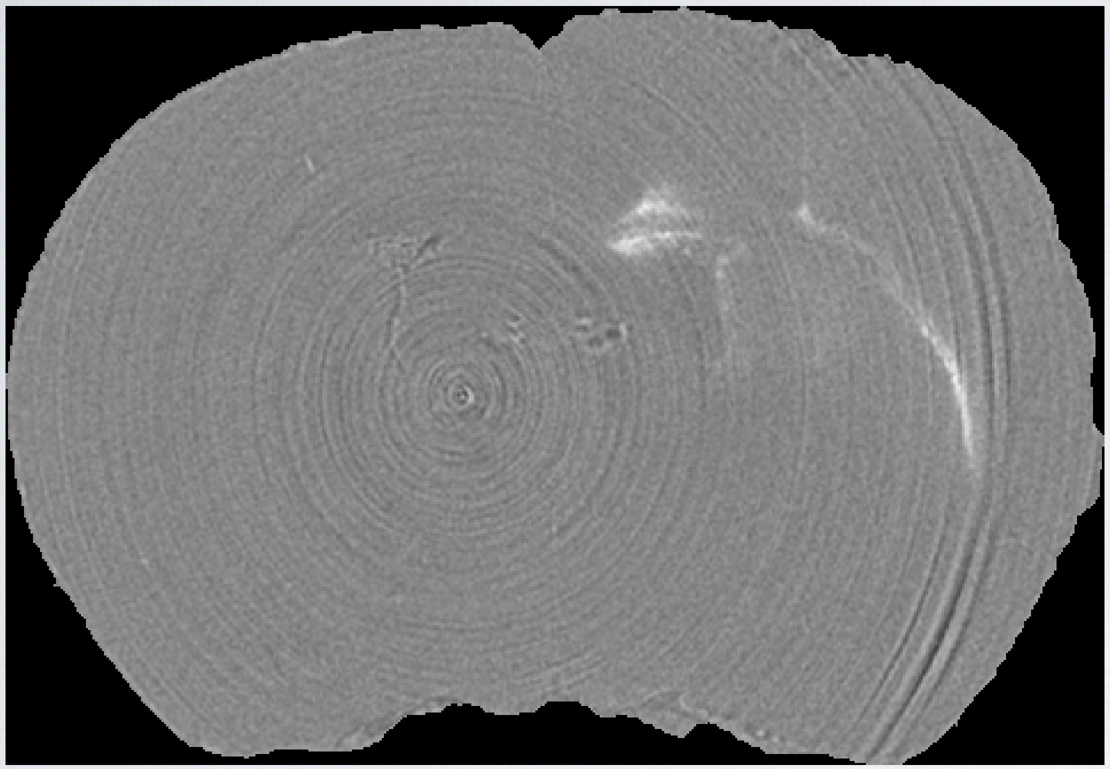
40 µm



How many USPIO-labeled macrophages are there?

How many USPIO-labeled macrophages are there?

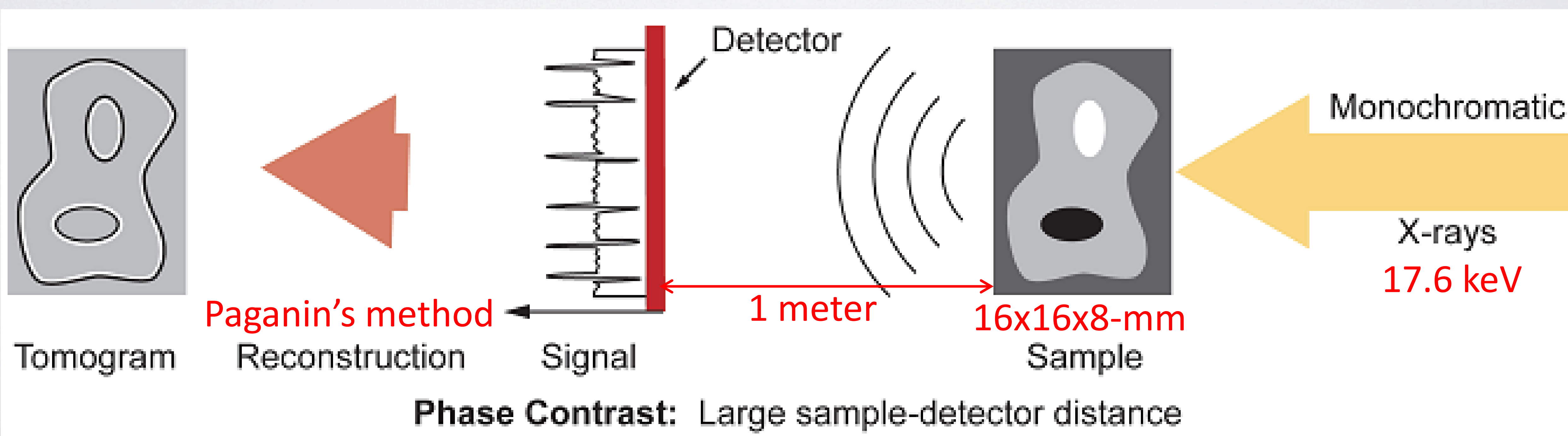
Team 4 (Tomographic imaging and therapy with radiation)
ID19 beamline (European Synchrotron Imaging Facility, Grenoble, France)



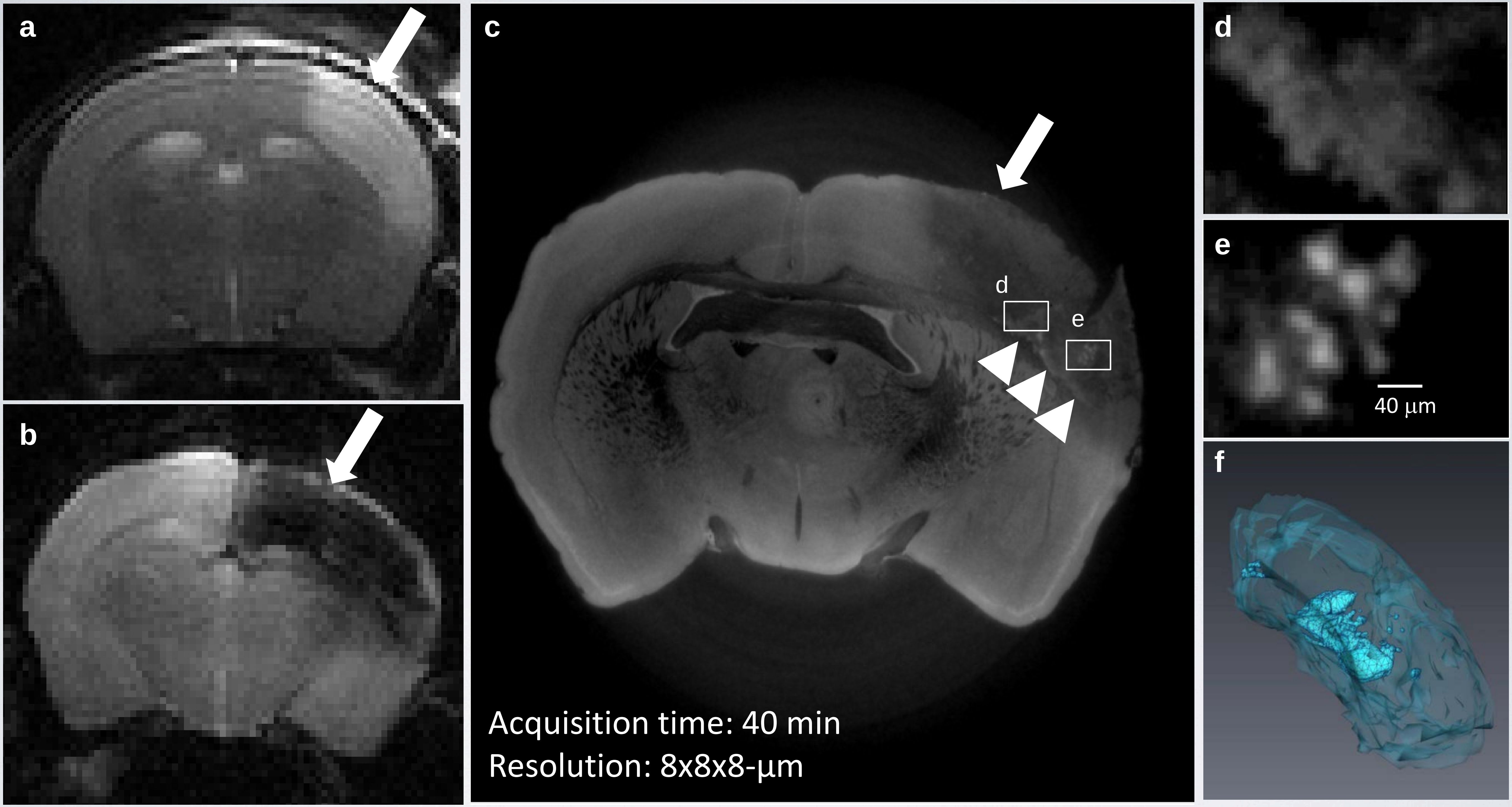
Absorption contrast with **Grating Interferometry**
(Acquisition time: 6 hours)

☺ USPIO detection
☹ Localization
☹ Quantification

Phase-contrast tomography



Synchrotron Radiation Phase Contrast Tomography (SR-PCT)

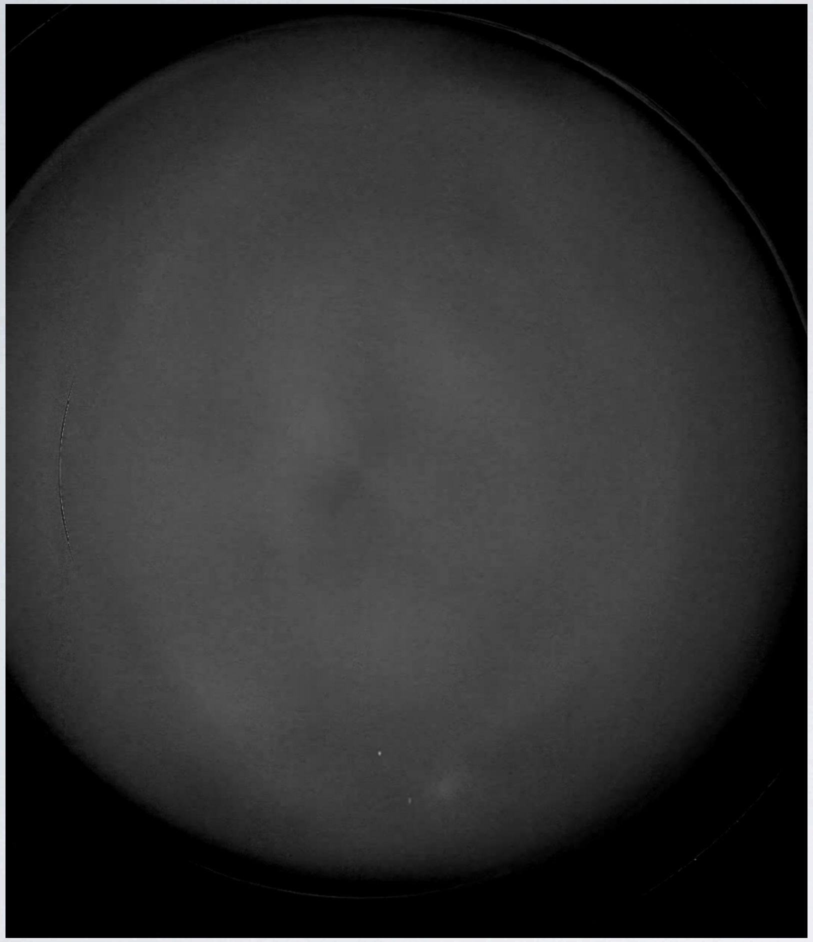


☺ USPIO detection

☺ Neuroanatomy in the intact brain

Marinescu et al., Mol Imaging & Biol 2013

Work in progress: image post-processing

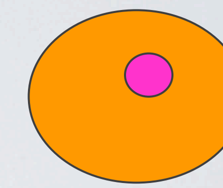


How many USPIO-labeled macrophages are there?

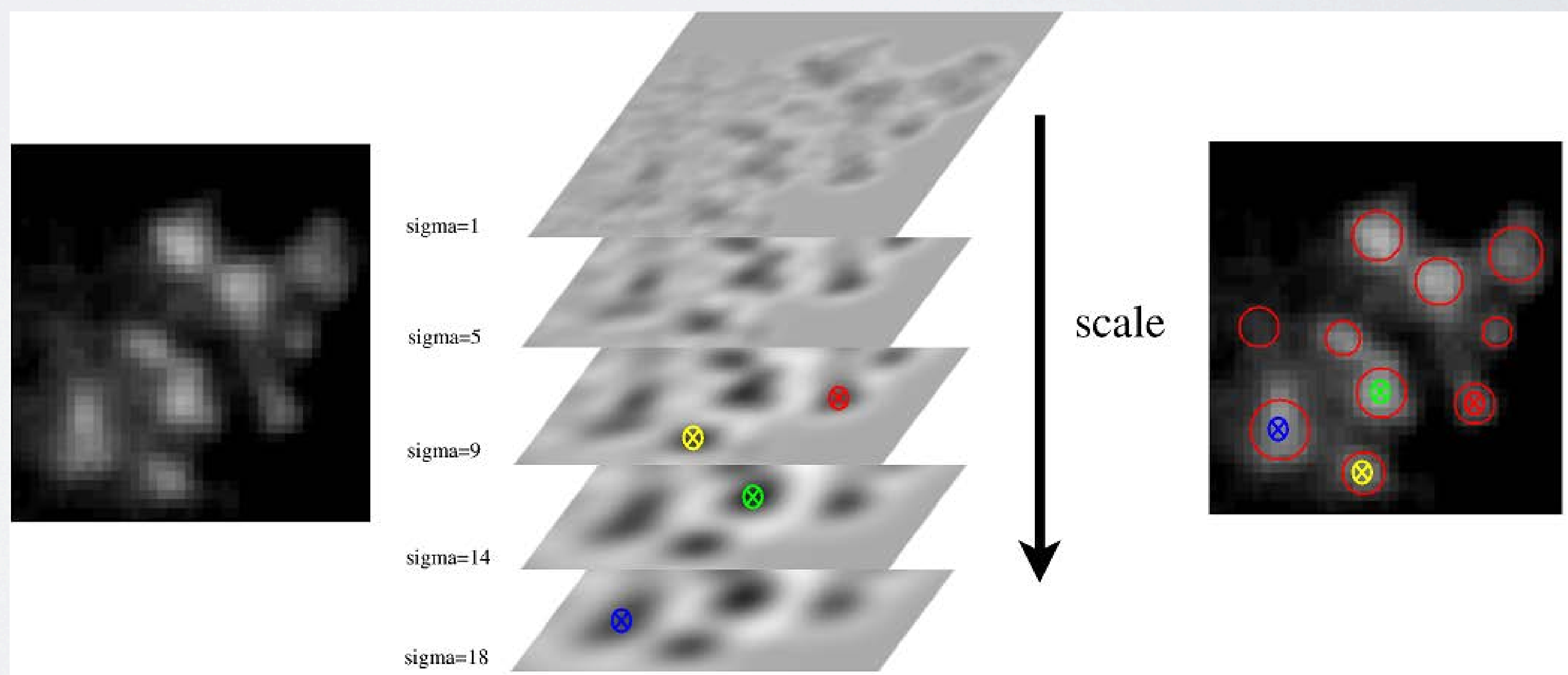
1000 images (2048x2048)
Manual segmentation is **time-consuming**

Team 6
(Cerebral imaging)

Blob detection



Rositi et al., Optics Express (submitted)

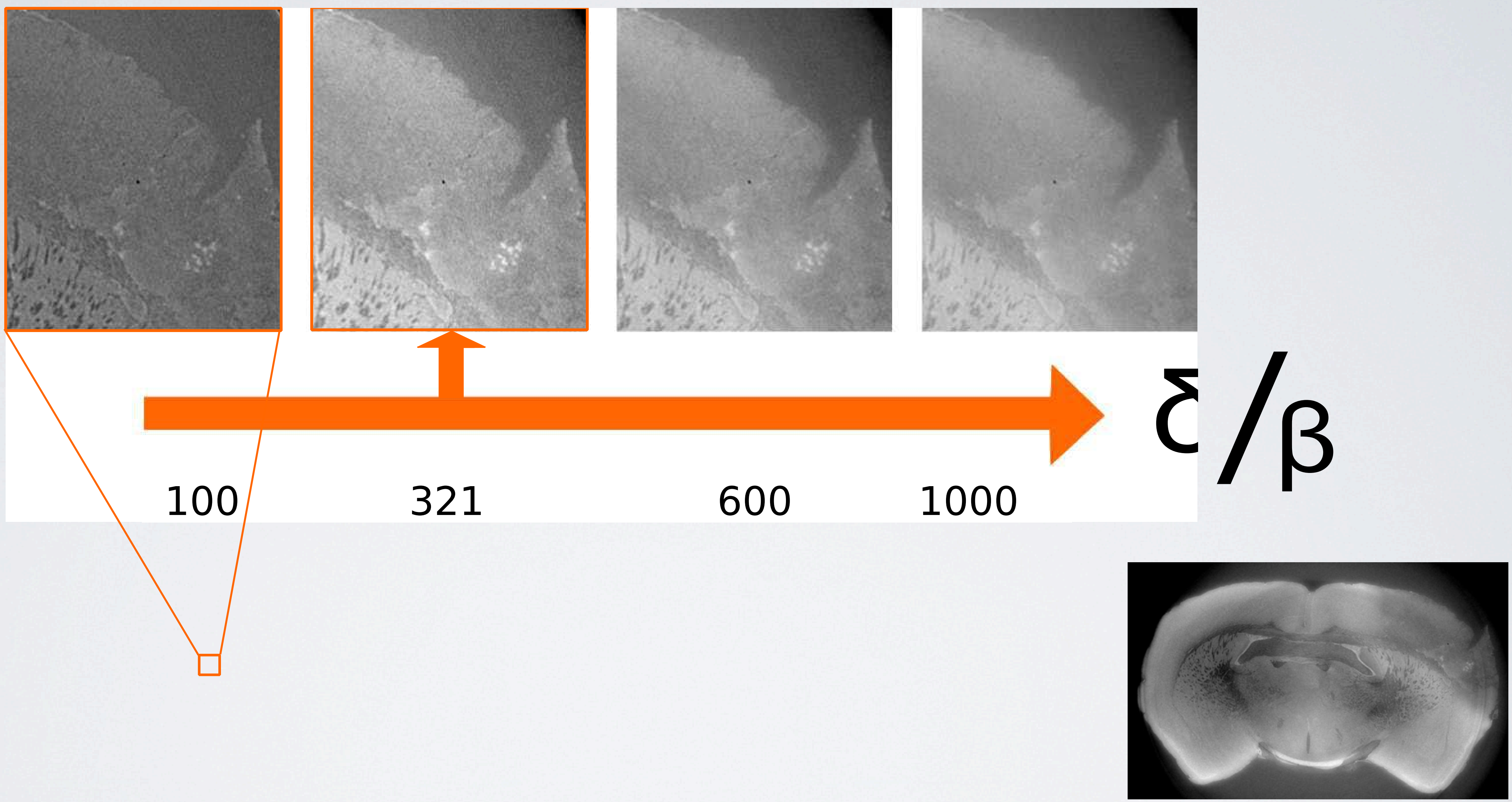


→ Validation using **simulations** with **noise modeling** from real data

Work in progress: image post-processing

Phase retrieval algorithm:

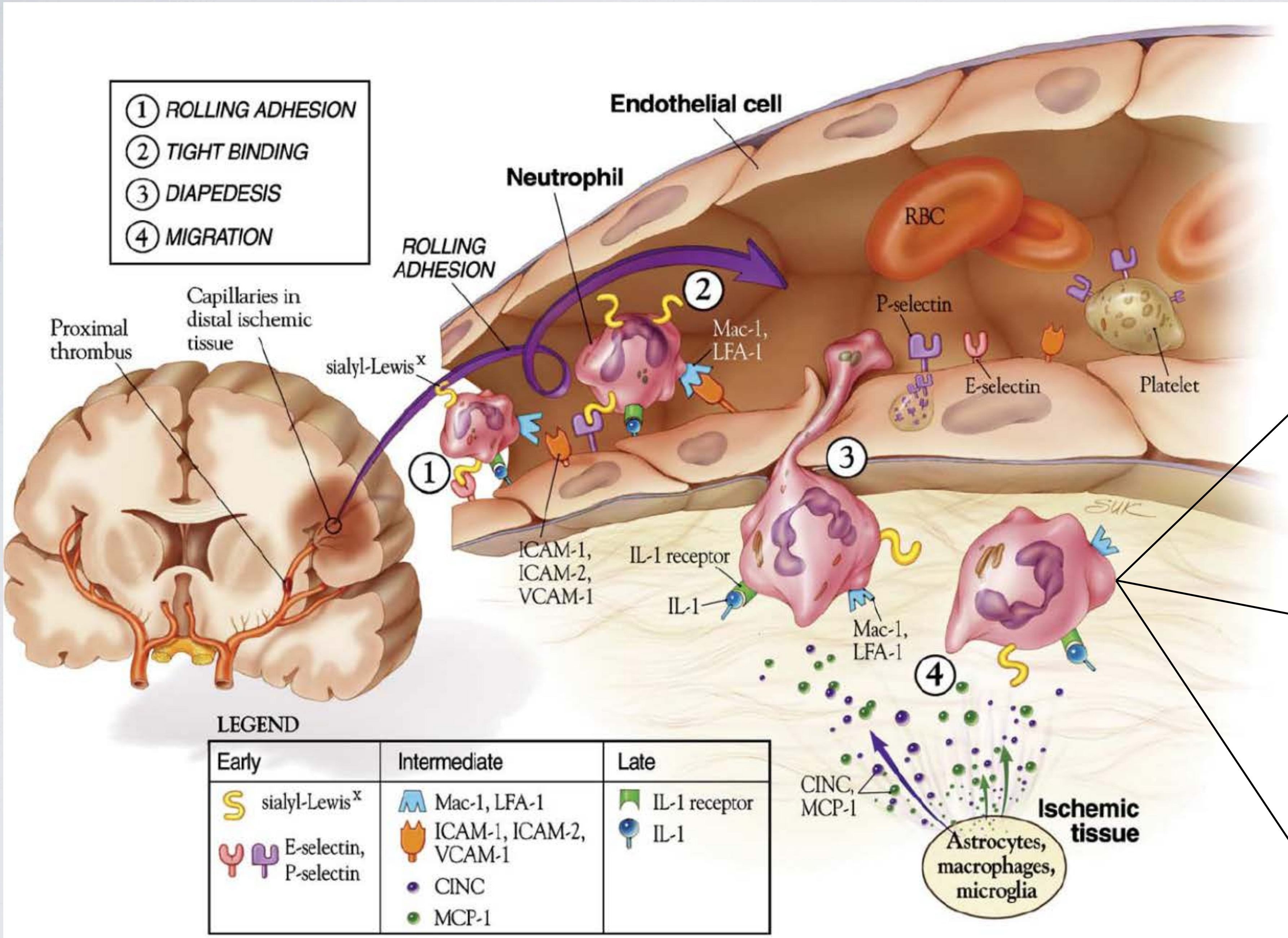
Paganin's method



δ real part and **β imaginary part** of the **refractive index** of the sample

Rositi et al., Optics Express (submitted)

Perspectives



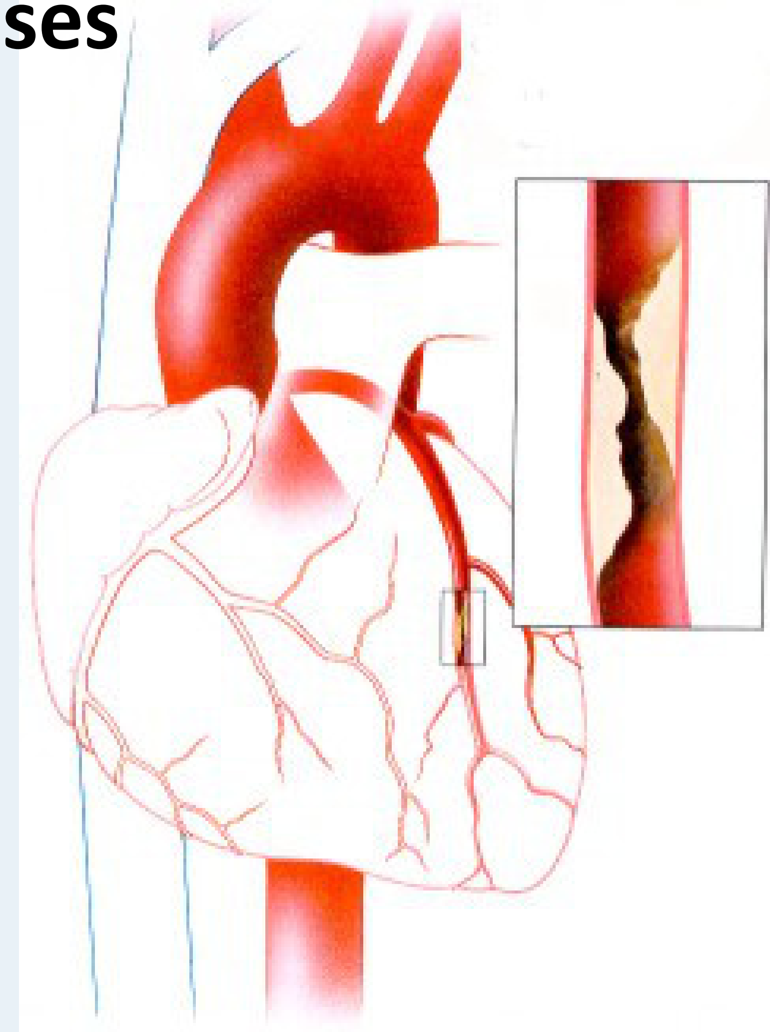
To image the **expression of CD11b *in vivo*** via a **trimodal targeted nanoparticle**
(collab. S Parola, Chemistry Lab, ENS Lyon, France)

→ Molecular imaging of neuroinflammation

Multimodal exploration of cardiac motion

- **Heart motion hampers:**
  - Image acquisition and quality
  - Image interpretation
  - Therapy implementation and evaluation

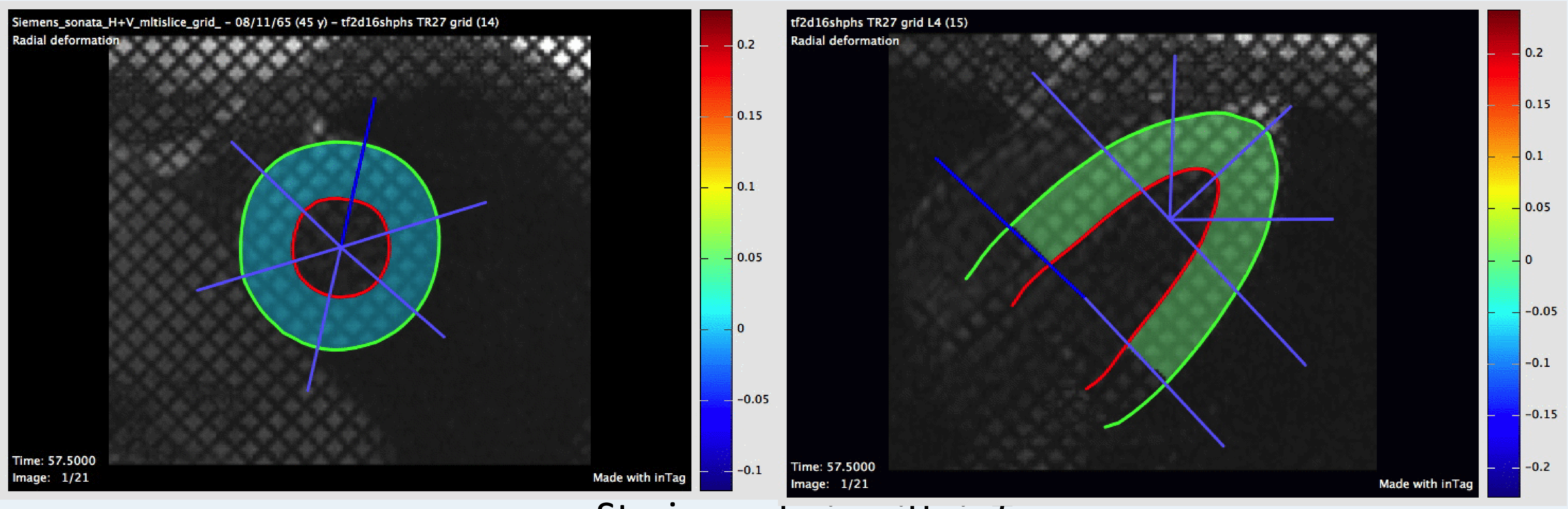
- **Heart motion is affected by ischemic heart diseases**



➔ It is important to quantify, interpret and monitor motion

Our achievements: Heart deformation in MRI (Teams 1 & 3)

- **Phase based motion estimation in tagged MRI**
  - *SinMod* method better than original *HARP [Arts et al., IEEE TMI, 2012]*
  - *inTag:* integrated analysis of tagged MR images. Free OsiriX plugin used by more than 200 centers

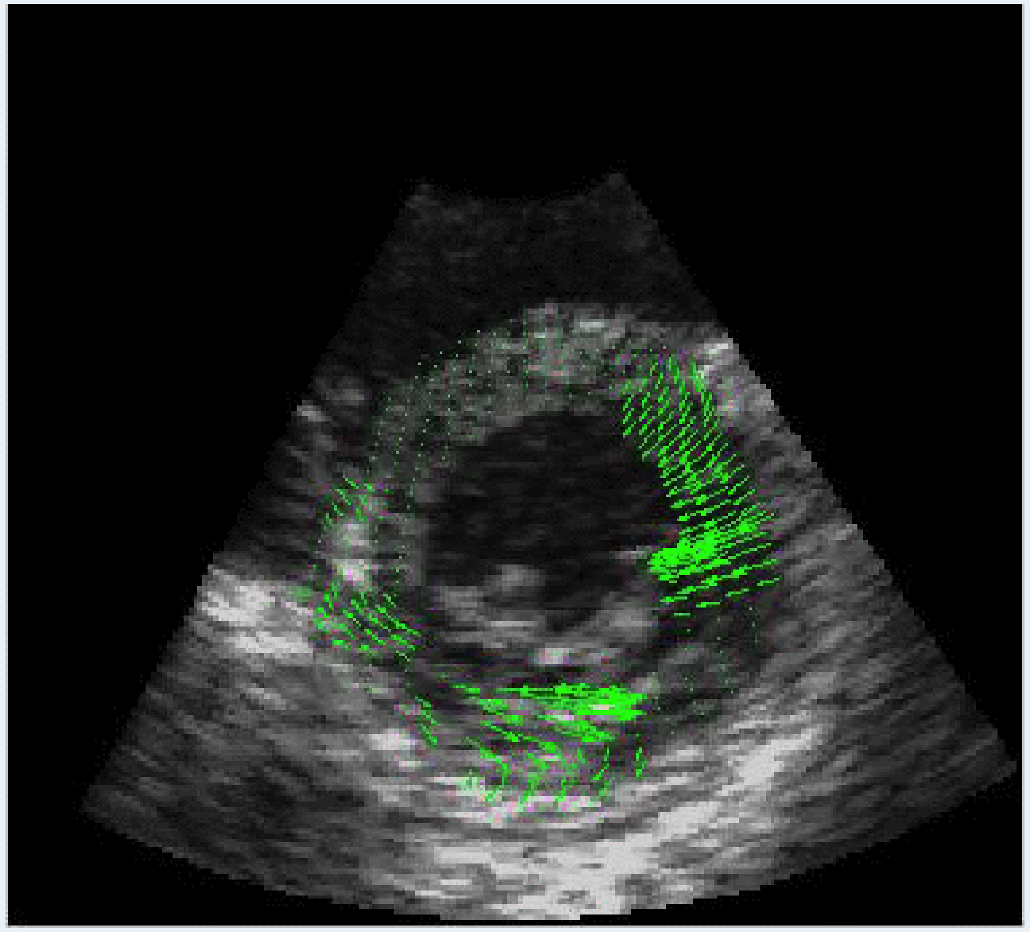


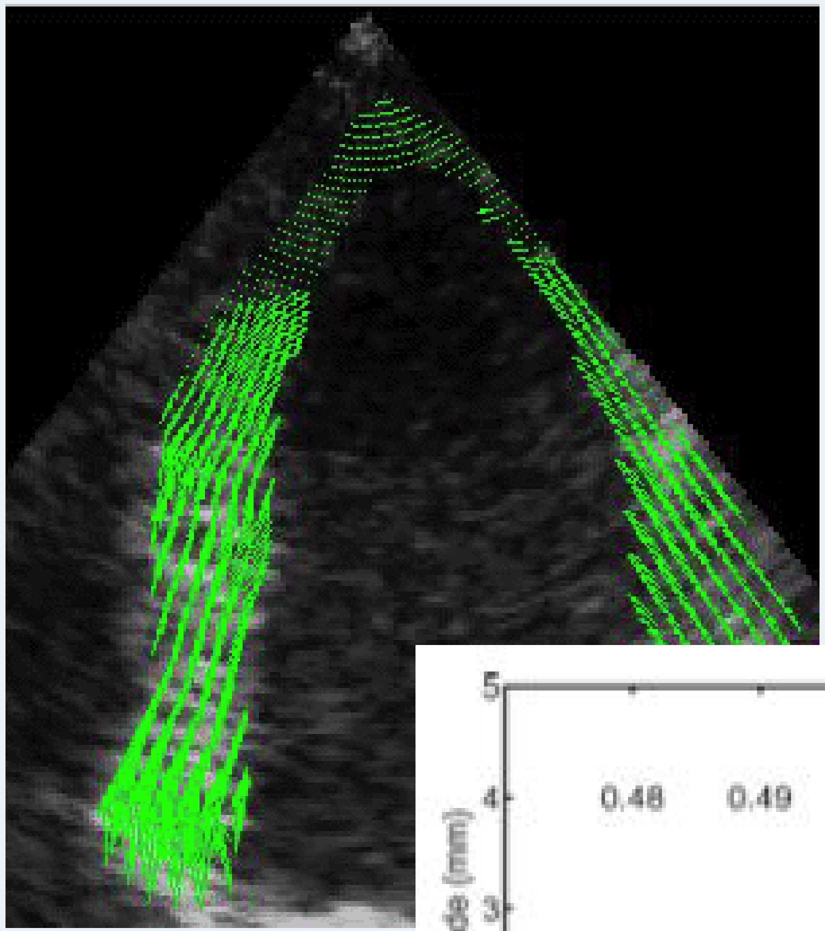
Strain analysis with *inTag*

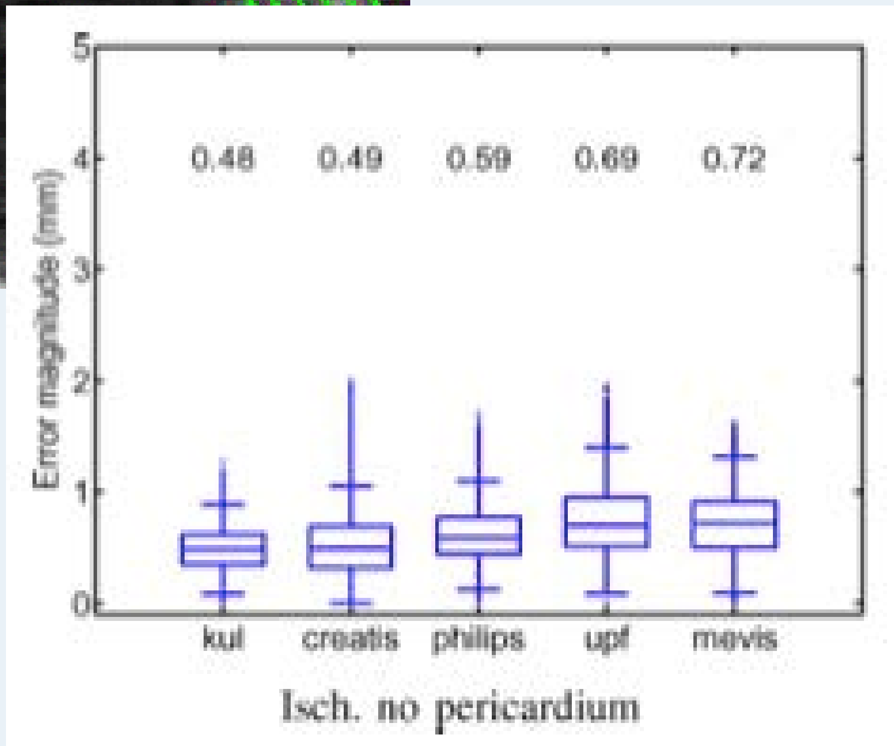
  - Other motion estimators:
    - o Phase based deformable block matching *[Basarab et al., TS, 2011]*

Our achievements: Heart deformation in US (Teams 2 & 3)

- **Monogenic phase based method** *[Alessandrini et al., IEEE TIP 2013]*





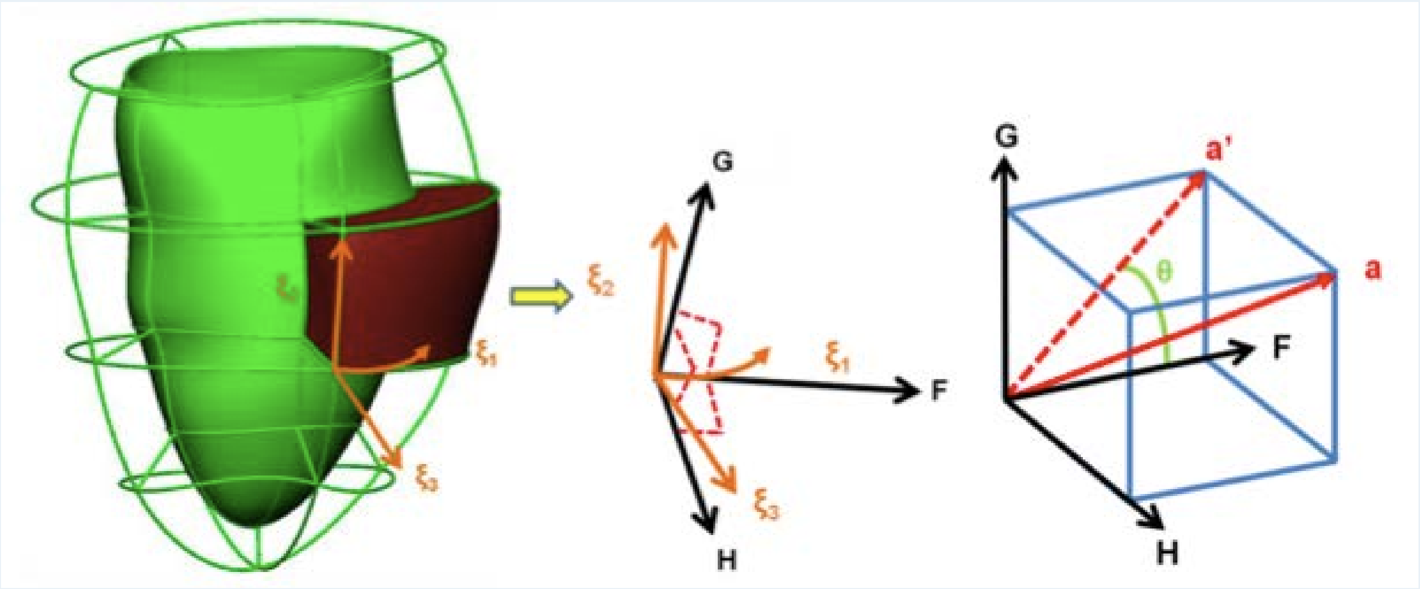


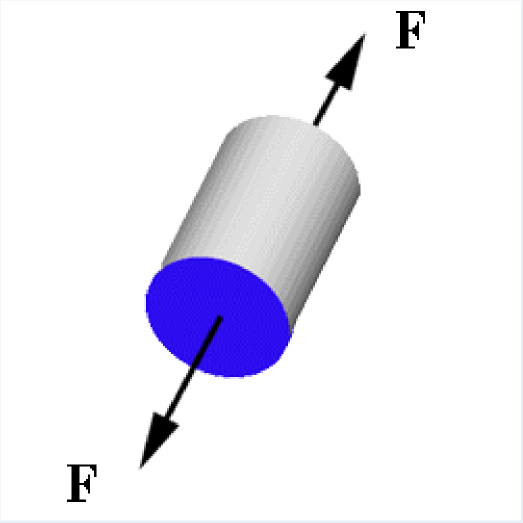
• Comparative evaluation on 3D-US realistic simulations: MICCAI 2012 challenge
[De Craene et al. IEEE TMI, 2013]

Myocardial motion characterization

- **'Classical' strain measurements**
  - Anatomical : circumferential, radial, longitudinal
  - Principal strains
- **3D torsion**
- **Fiber strain**
  - Can be more relevant than current measurement of chamber function
  - Provide insights to sarcomere mechanical behavior
  - May allow better understanding of disease mechanisms at tissue level.

➔ However not directly accessible: require the fibers' direction





On going work: myocardial fiber strain

1. *In vivo* Tagged MRI Analysis

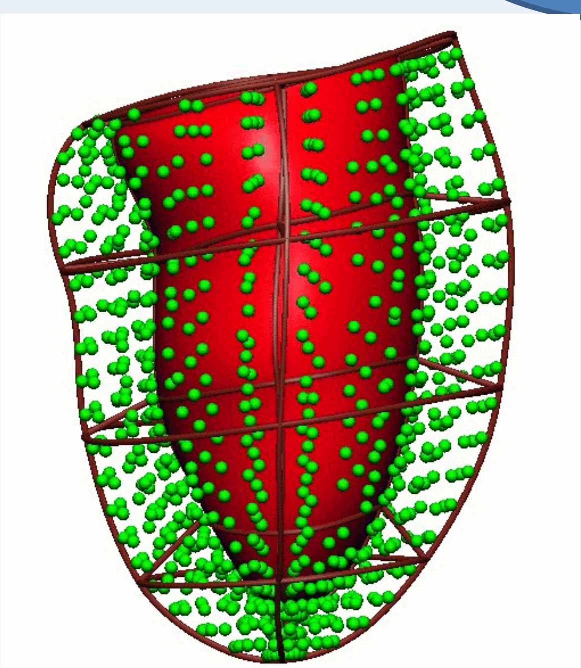
- Extract *in vivo* LV geometry and motion to generate personalised FE model of LV kinematics

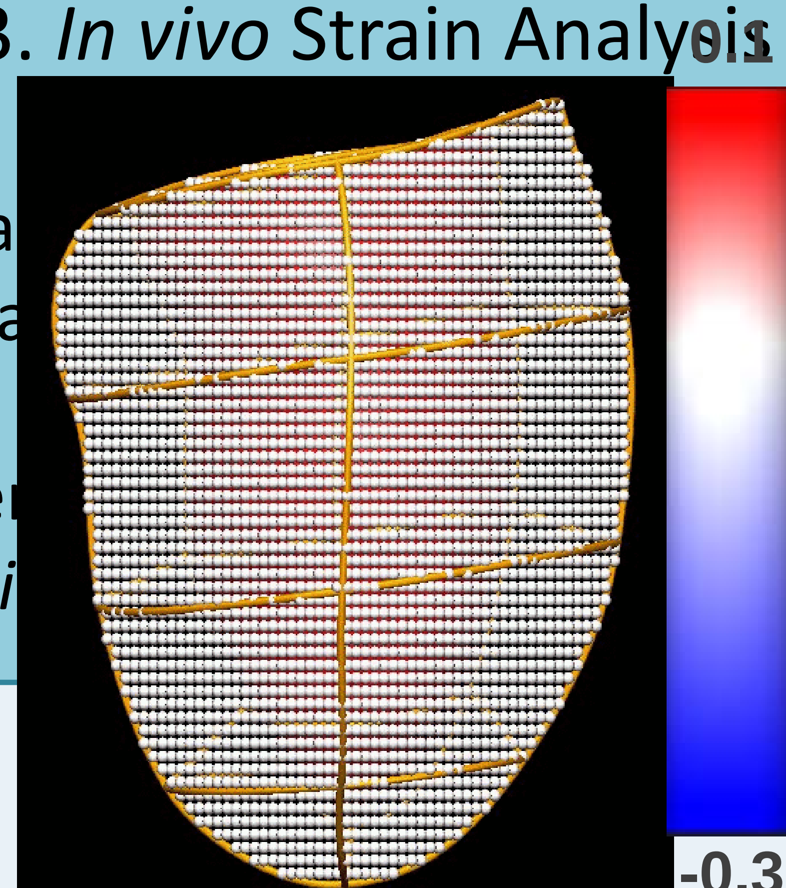
2. *Ex vivo* DTMRI Analysis

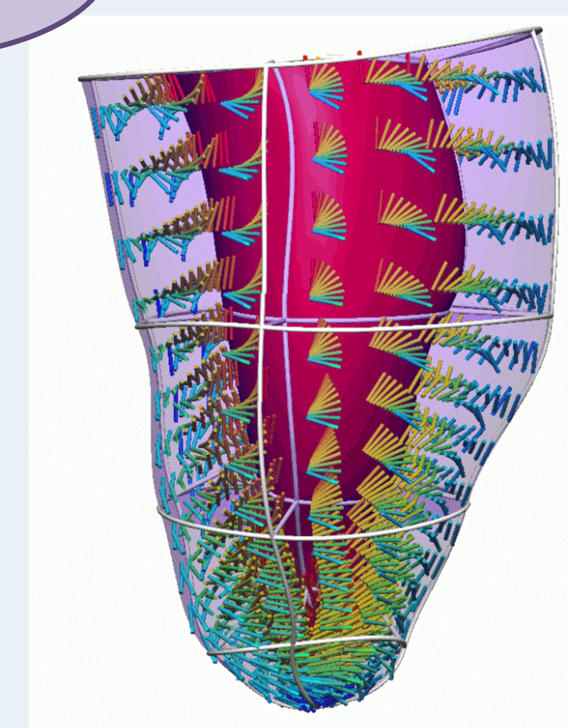
- Extract *ex vivo* LV geometry and fibre orientations
- Integrate fibre orientation data into the *in vivo* LV FE model

3. *In vivo* Strain Analysis

- Extra… integra… …el
- Dete… …ility in *in vi*…

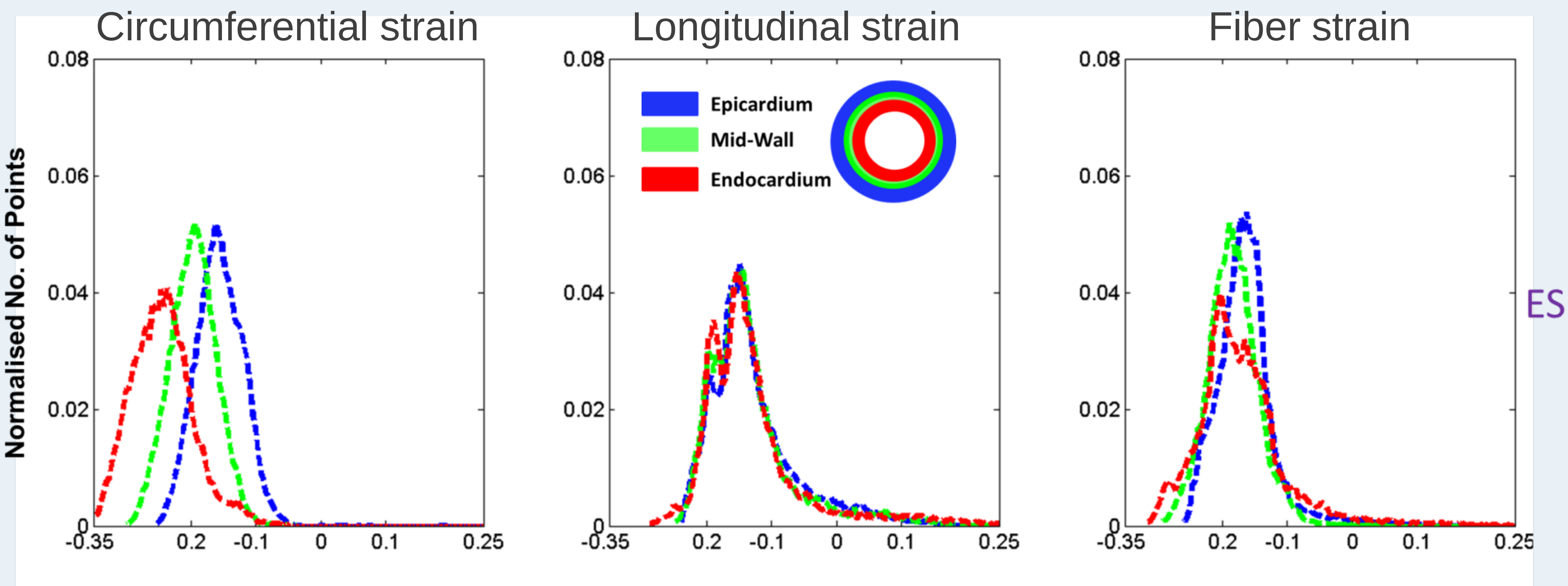






collab. Auckland Bioengineering Institute

Fiber strain



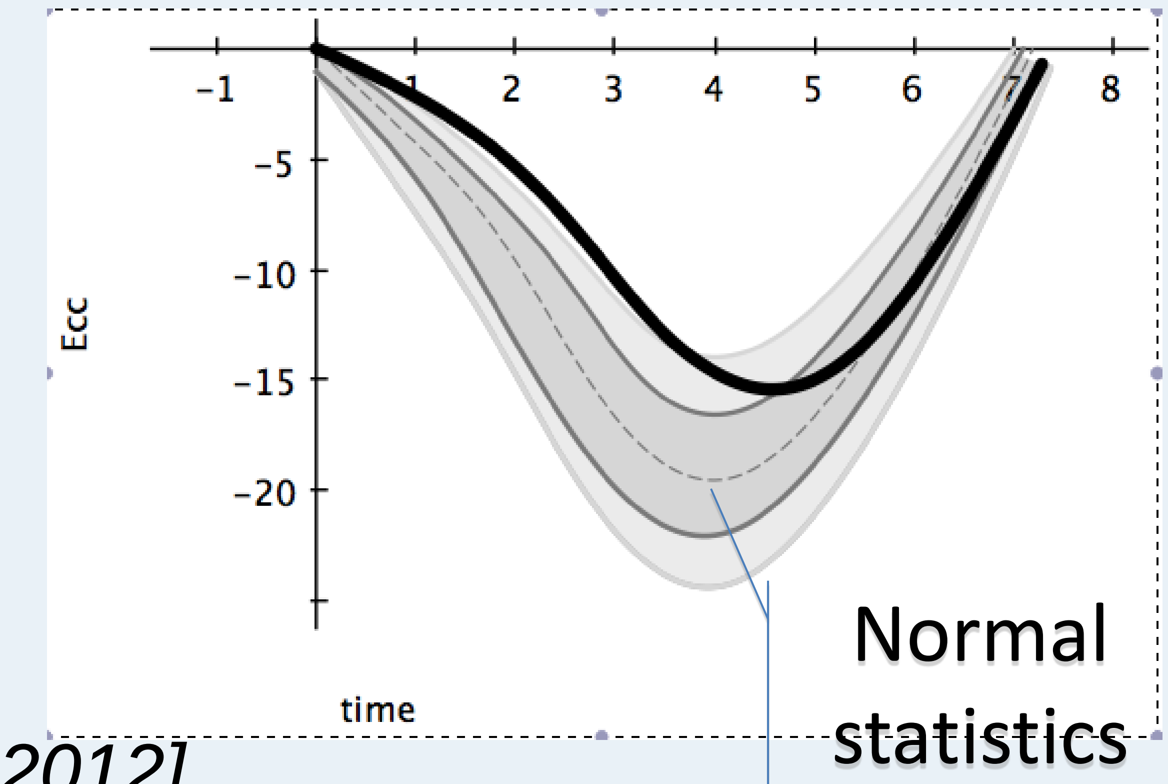
Experiments on 3 TMRI / 7 DTMRI

- Fibre strain estimation is not sensitive to the degree of variation of fibre structure (±13º) among individuals.
- Transmural difference in mean fibre strain is indeed equalised at ES for all 7 DTMRI cases.

[Casta et al, FIMH’13], [Wang et al, ISBI 2012]

On going: statistical atlases of ‘normality’

- **‘Normal’ strains: through the *inTag* software agreement**
  - More than 300 examinations collected
  - Organized by age and gender
  - Circumferential, radial, longitudinal, principal strains
  - Analysis in the context of the 3dStrain ANR project (2011-2015)

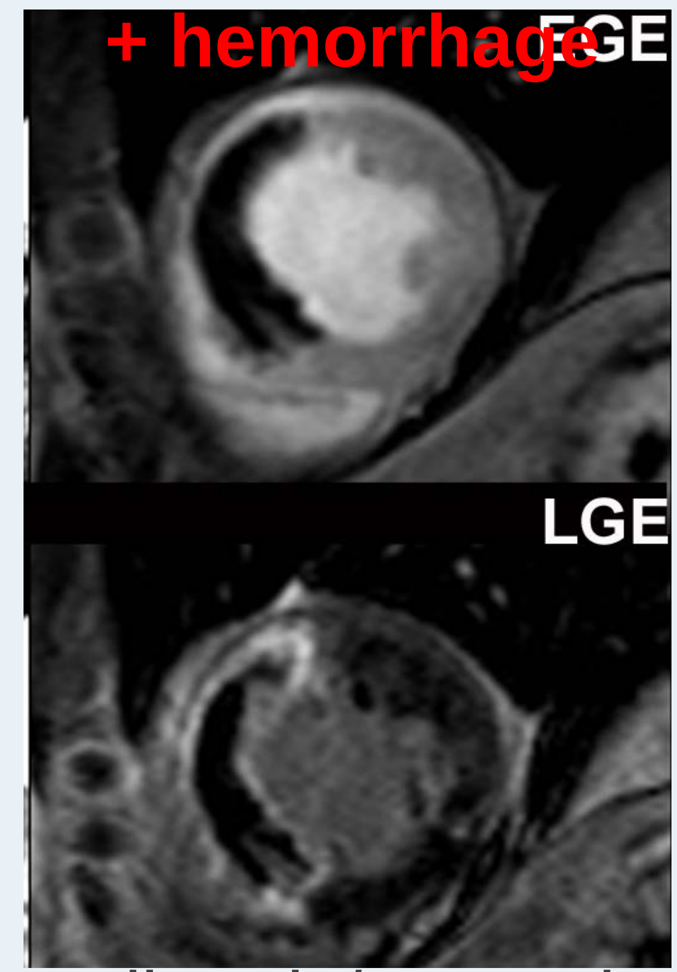


- **Cardiac fiber architecture:**
  - DTI based: *[Lombaert et al. IEEE TMI 2012]*
  - DWI based: in progress
- **Fiber strain**
  - Methodology: *[Casta et al, FIMH’13], [Wang et al, ISBI 2012]*
  - Issue: increase the number and quality of DTI-Tag data pairs

Perspectives (Team 1, 2 & 3):

- **Investigation of new motion estimators**
  - Analytic, monogenic, structure tensor, optimal transport
- **Full 3D Strain estimation: MRI (Cine, tag, Dense), US**
- **Strain based characterization of pathological myocardium**
  - Initially proposed for elasticity based tissue inclusions segmentation in atherosclerotic plaque *[Le'Floch, UMB, 2012]*
  - Takes into account fiber architecture
- **Relation between tissue and function**
  - Tissue characterization from MRI cardiac imaging

No reflow lesion
+ hemorrhage



Fibrosis/Necrosis
+hemorrhage

Perspectives: Intra-thoracic diagnostic and Therapeutic Imaging (Teams 1, 2, 3 & 5)

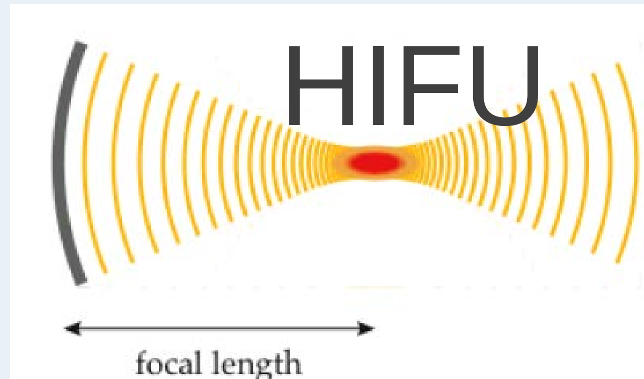
- **Diagnostic imaging + therapy with on line motion monitoring**

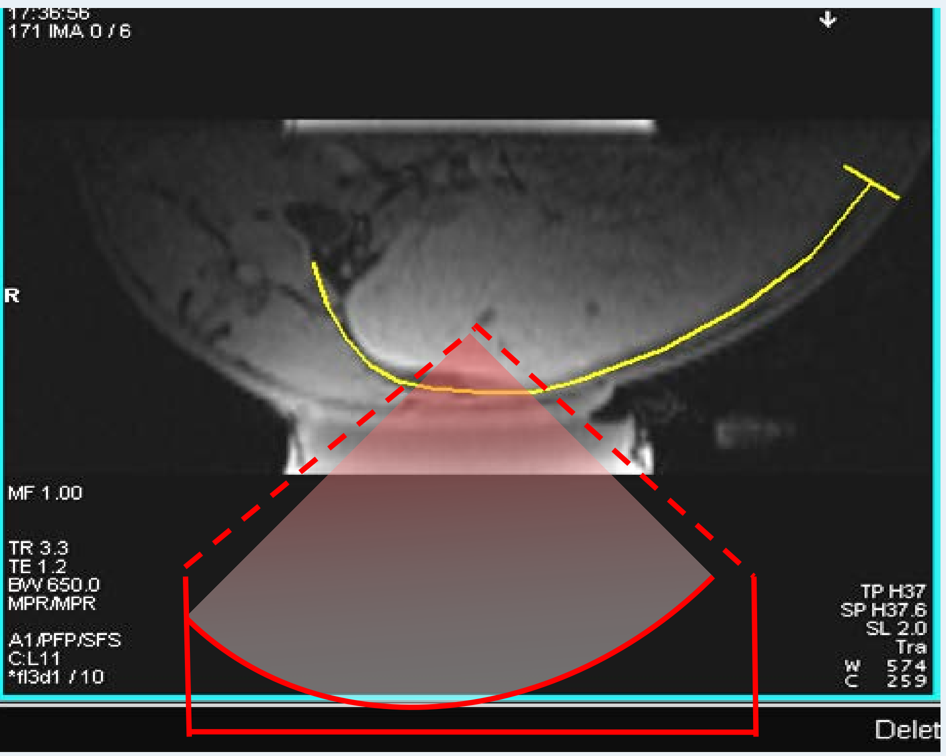
- **The example: MRgHIFU therapies in the thorax**
  - -lung tumor ablation
  - -cardioprotection in acute reperfused myocardium

- **New multimodal MRI-US-PET approach**
  - ➔ Device developments: US transducers compatible with MRI/PET
  - ➔ respiratory and cardiac motion handling

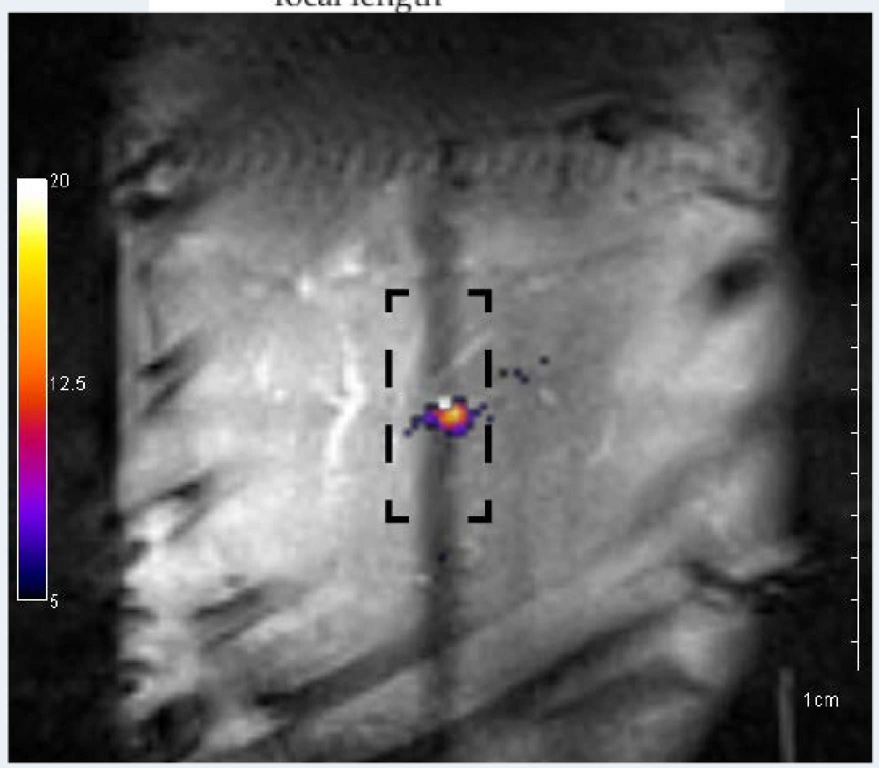
- **Intra-thoracic Multimodal and Therapeutic Imaging project**:
  - Has been approved by Pôles de Compétitivité Régionaux VIAMECA in 2012-2013 and LYONBIOPOLE en 2013
  - Rewarded by trophée CANCEROPOLE Régional CLARA, 2012
  - Collab HUG, Geneva
  - LABEX: PRIMES, CeLyA, IHU OPeRa; EquipEx LiLi (hybrid MRI-PET system)

HIFU Thermotherapy of mobile organs under MR/US guidance

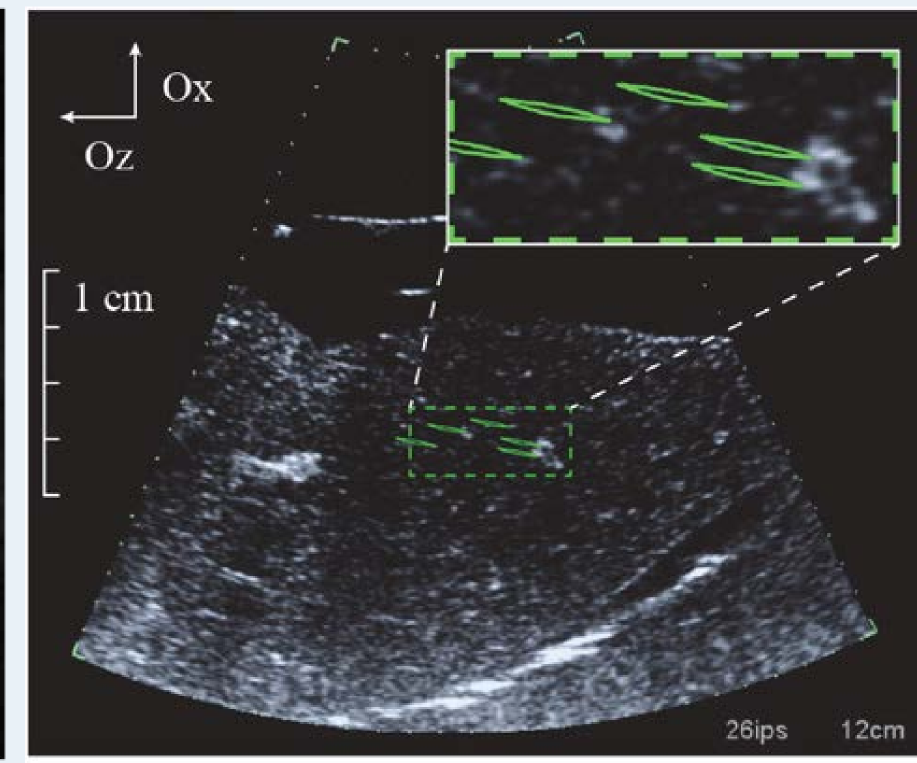




Target localization in MRI



Thermal ablation under MR thermometry (accuracy <1°C)



Real time tracking with US and monitored MRI

Courtesy Auboiroux V., Petrusca L., Salomir S., Viallon M., HUG.

Open discussion…