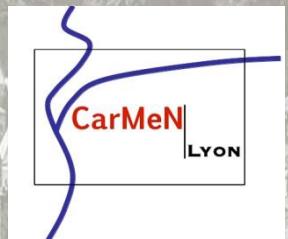




Potentiel de la TEP/IRM clinique et des nouveaux agents d'imagerie en cardio-vasculaire

Emmanuelle Canet Soulas

Laboratoire CarMeN, Université de Lyon



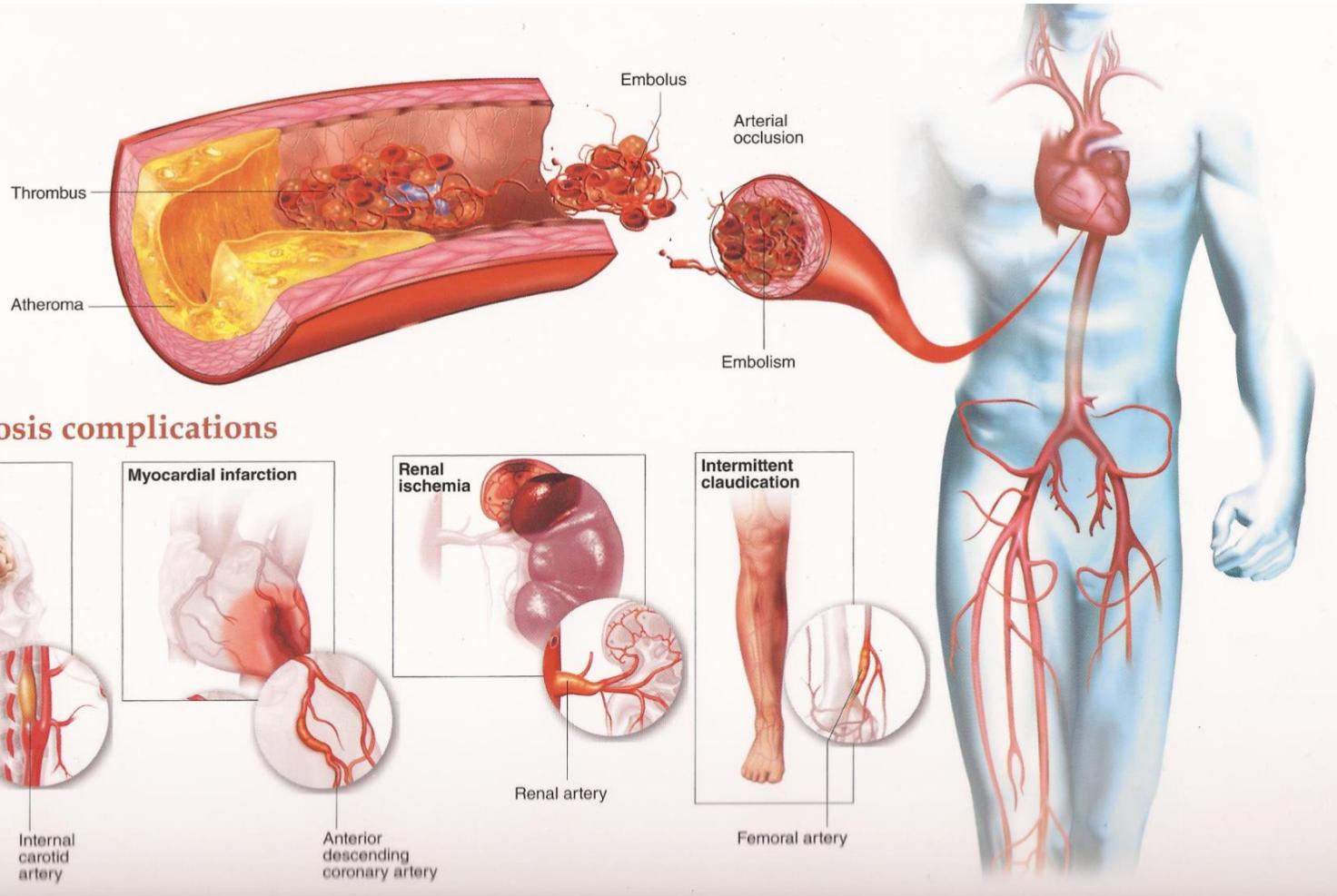


TEP/IRM de l'athérosclérose

- Enjeu clinique : marqueurs pour la décision thérapeutique (médicale ou interventionnelle)
- Place de l'IRM
- Place de la TEP
- Essais TEP/IRM translationnels



L'Athérosclérose : une maladie vasculaire multi-sites





Caractéristiques de la plaque vulnérable

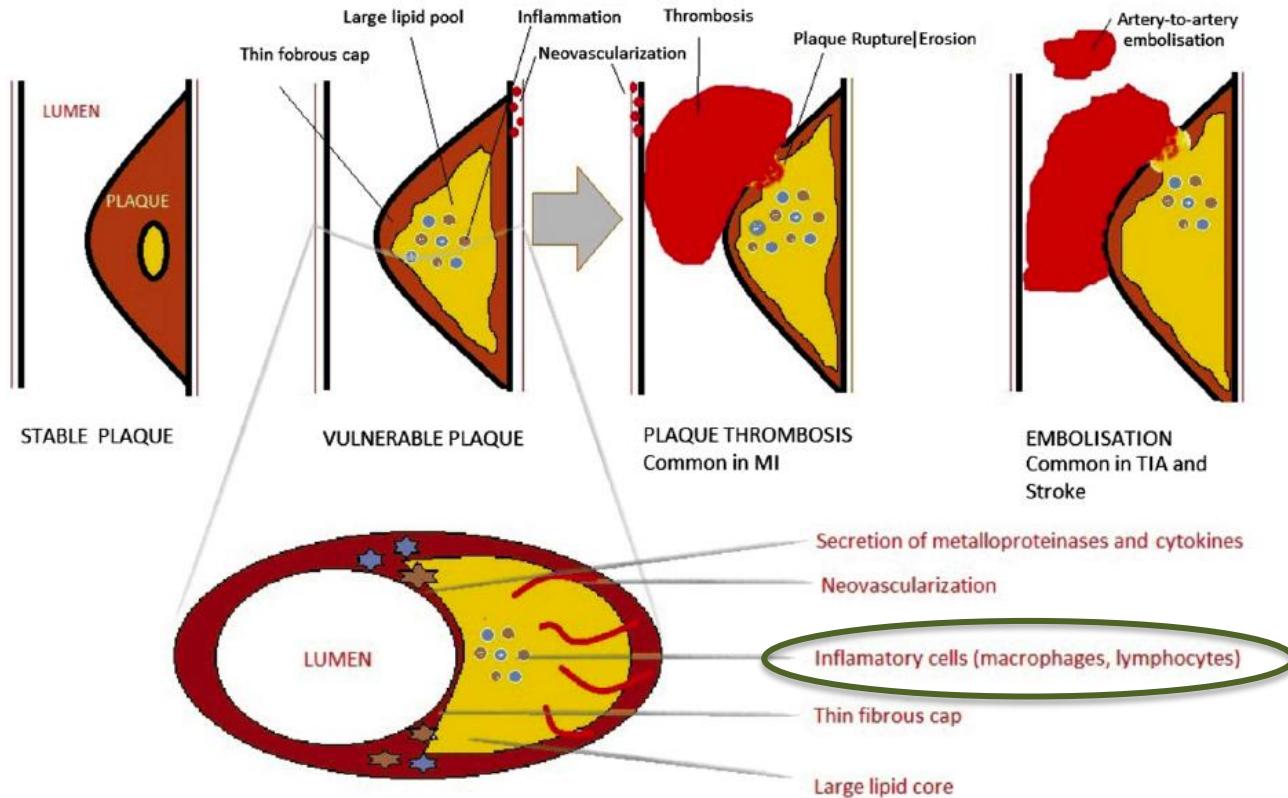


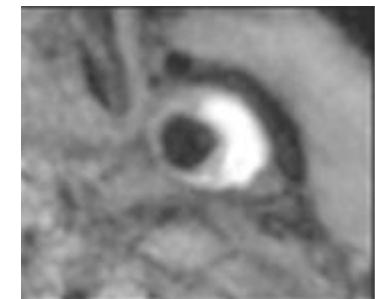
Fig. 1. Pathomechanisms of cardiac and cerebral acute events in coronary and carotid atherosclerosis, and features of stable and vulnerable plaques.

Jashari F et al, *Atherosclerosis*, 2013



Marqueurs cliniques d'imagerie Aujourd'hui et demain

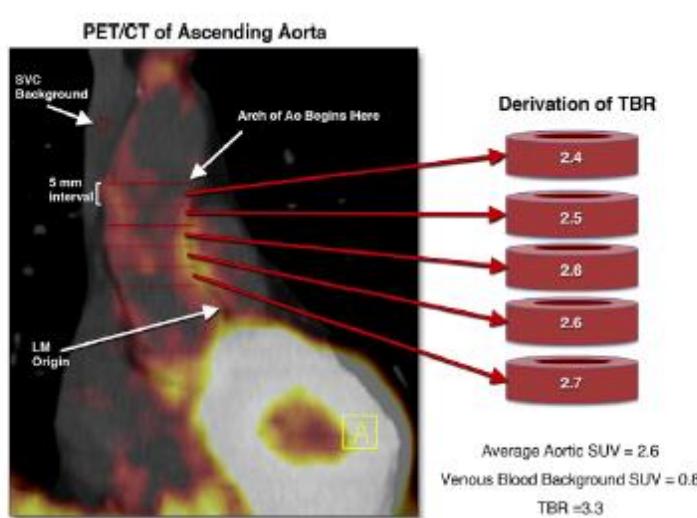
- **IRM 3D haute résolution de la carotide**
- Approche multimodale en étude prospective
 - Echographie
 - Doppler Transcranien pour la détection des emboles
 - IRM haute résolution et IRM fonctionnelle
 - Marqueurs biologiques
- **Potentiel clinique de la TEP/IRM (score de vulnérabilité)** : TEP de l'inflammation et IRM dynamique de contraste



*Calcagno C, Ramachandran S, Millon A, et al, Curr Cardiovasc Imaging Rep. 2013
Rosenbaum D, Millon A, Fayad ZA. Curr Atheroscler Rep. 2012*

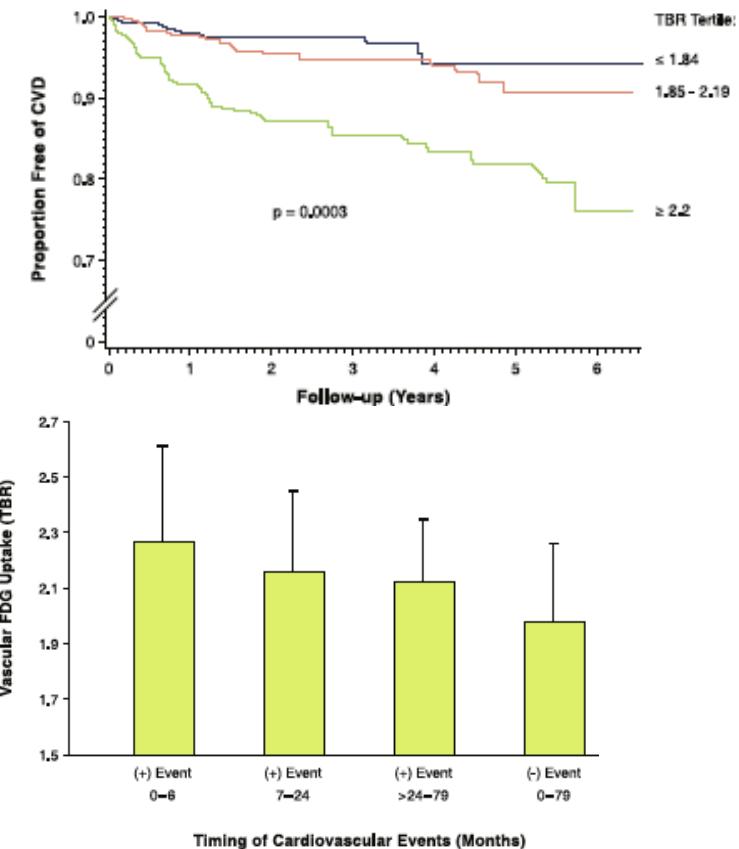


18F-FDG : la référence de l'imagerie de l'inflammation dans l'athérosclérose



High risk TBR >2.2

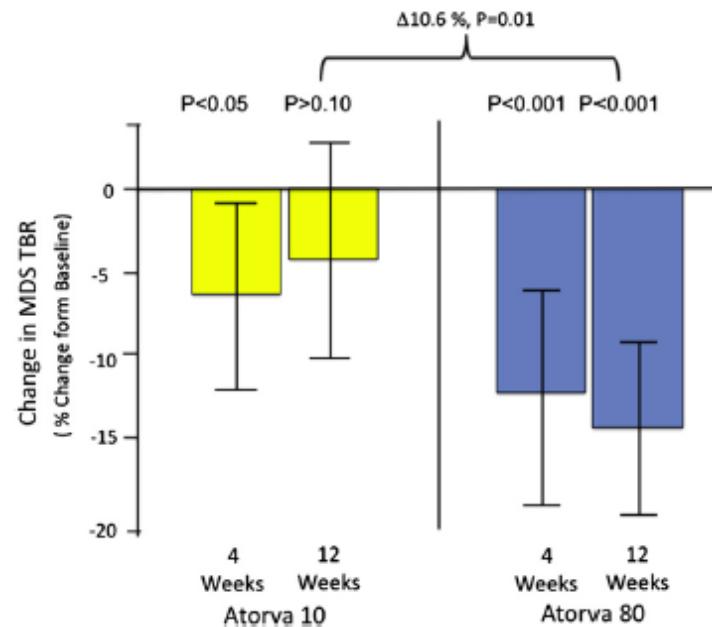
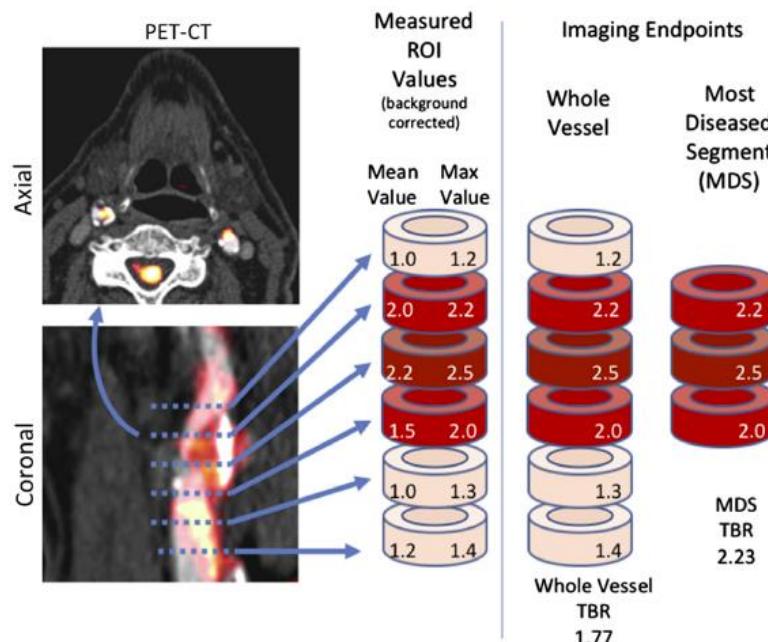
Low risk TBR <1.84



Figueroa AL et al, JACC, 2013



18F-FDG : la référence de l'imagerie de l'inflammation dans l'athérosclérose



MDS: most diseased segment
right and left carotid and aorta

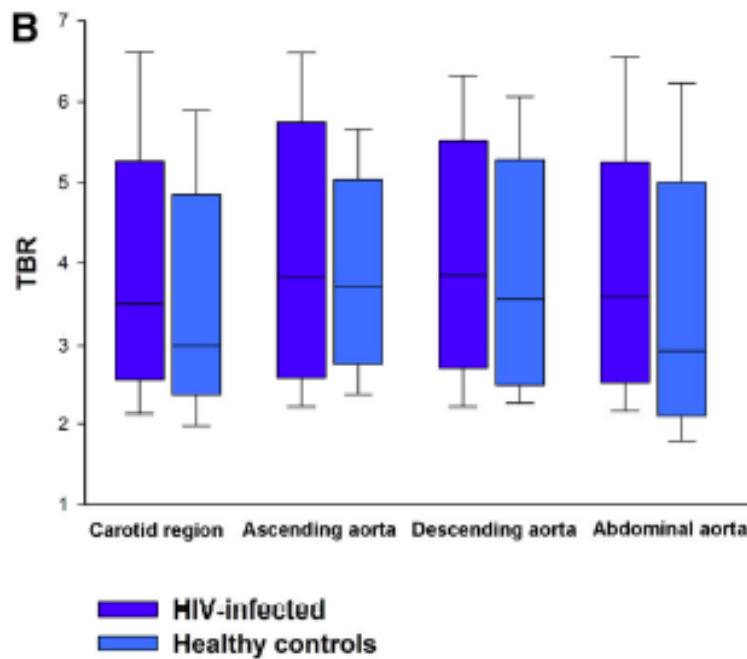
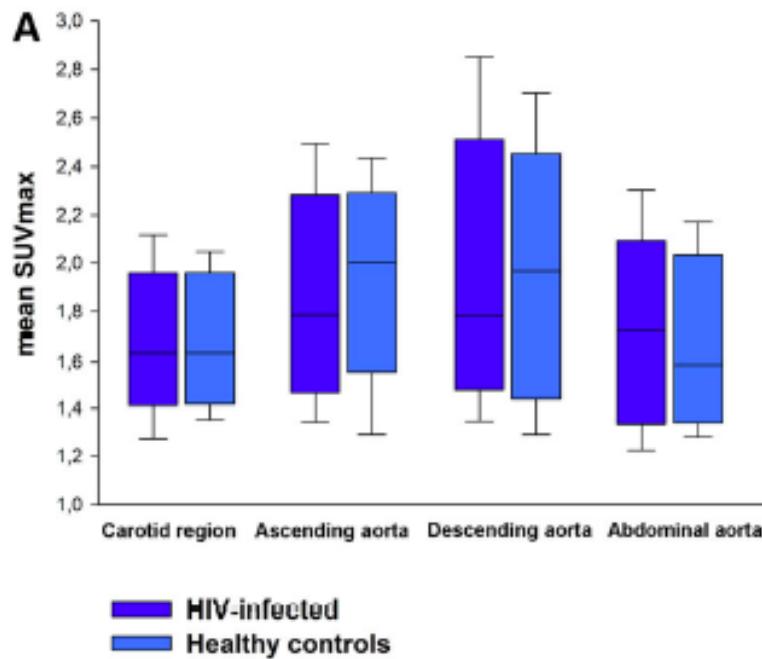
High risk TBR >2.2

Low risk TBR <1.84

Tawakol A et al, JACC, 2013



18F-FDG: des limites?



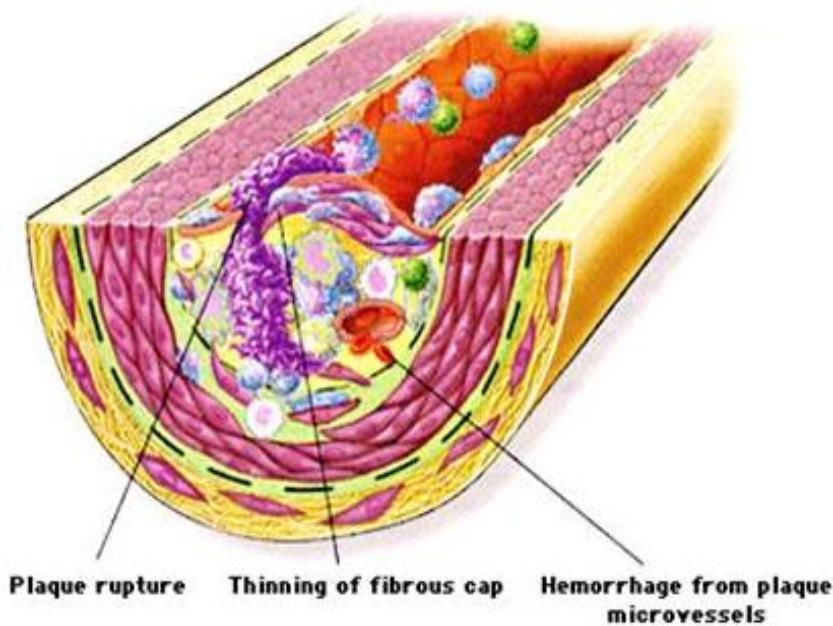
Multi-vessel analysis in HIV-infected patients vs healthy controls

High risk TBR >2.2
Low risk TBR <1.84

Knudsen A et al, J Nucl Cardiol, 2015

Imagerie clinique de l'athérosclérose

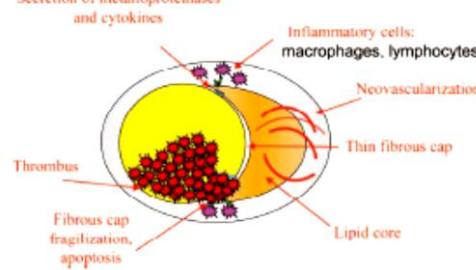
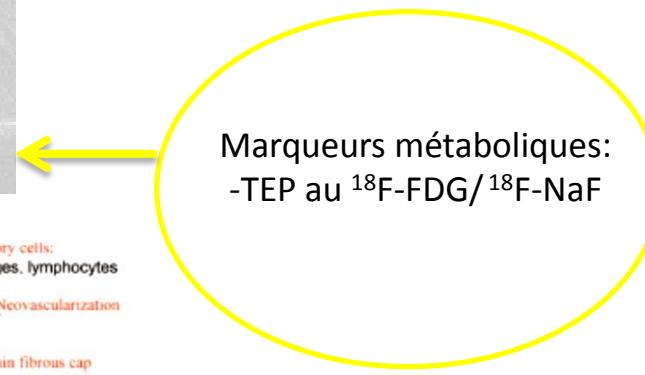
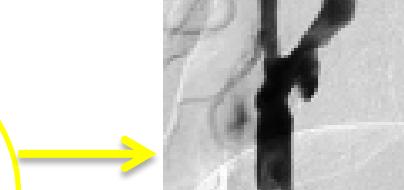
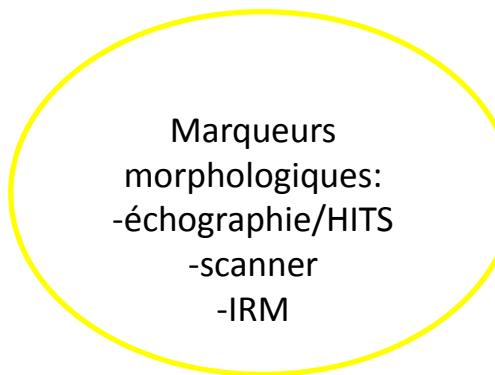
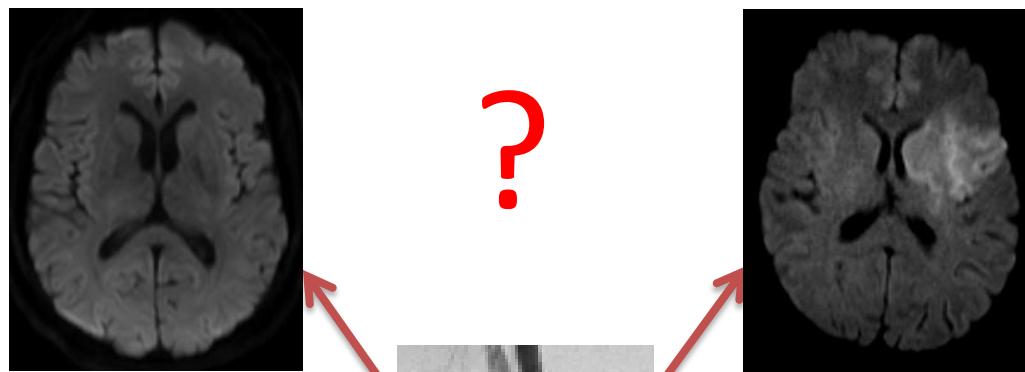
Au-delà du FDG, quel marqueur pour la plaque vulnérable?





Imagerie clinique de l'athérosclérose

Plaque carotidienne asymptomatique : l'enjeu



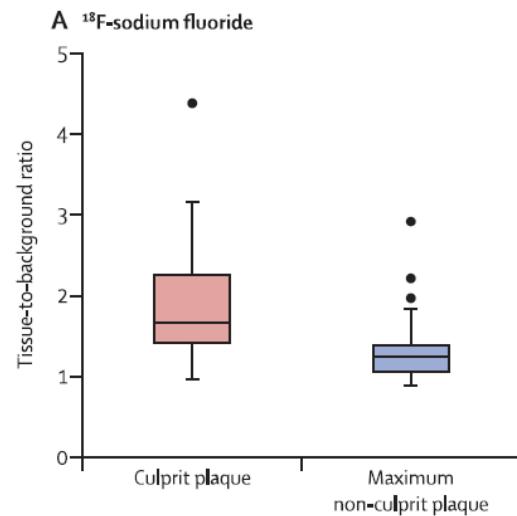
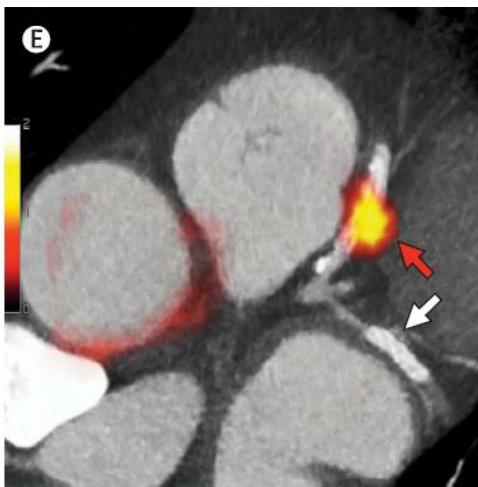
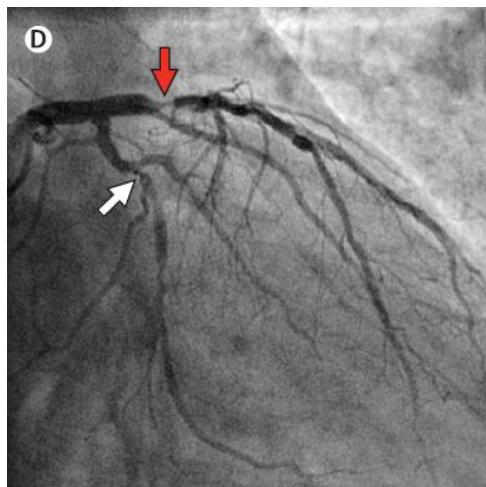
Nighoghossian, Stroke 2005



- Fixation du ^{18}F -NaF au niveau des plaques coronariennes

(*Joshi, Lancet 2014*)

- N=40 sujets avec infarctus du myocarde récent
- Fixation au niveau de la plaque coupable: 37/40 patients
- Fixation plus intense au niveau de la plaque coupable vs plaque non coupable (TBR max 1,66 vs 1,24, $p<0,001$)



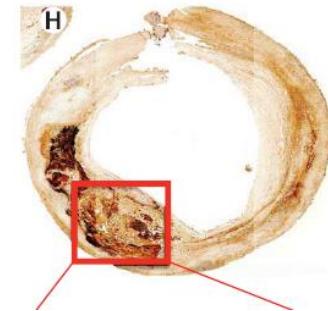
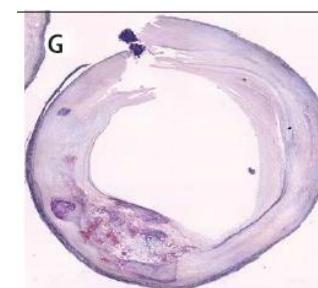
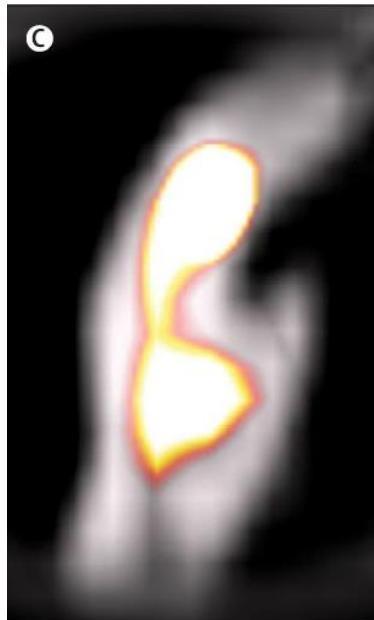
Joshi, Lancet 2014



- Corrélation fixation $^{18}\text{F-NaF}$ /anatomo-pathologie

(*Joshi, Lancet 2014*)

- 12 plaques CI symptomatiques (10-27j)
- Fixation de $^{18}\text{F-NaF}$ associée à
 - activité de calcification
 - infiltration macrophagique
 - apoptose
 - cœur nécrotique



Joshi, Lancet 2014



Vulnérabilité de la plaque: intérêt du $^{18}\text{F-NaF}$

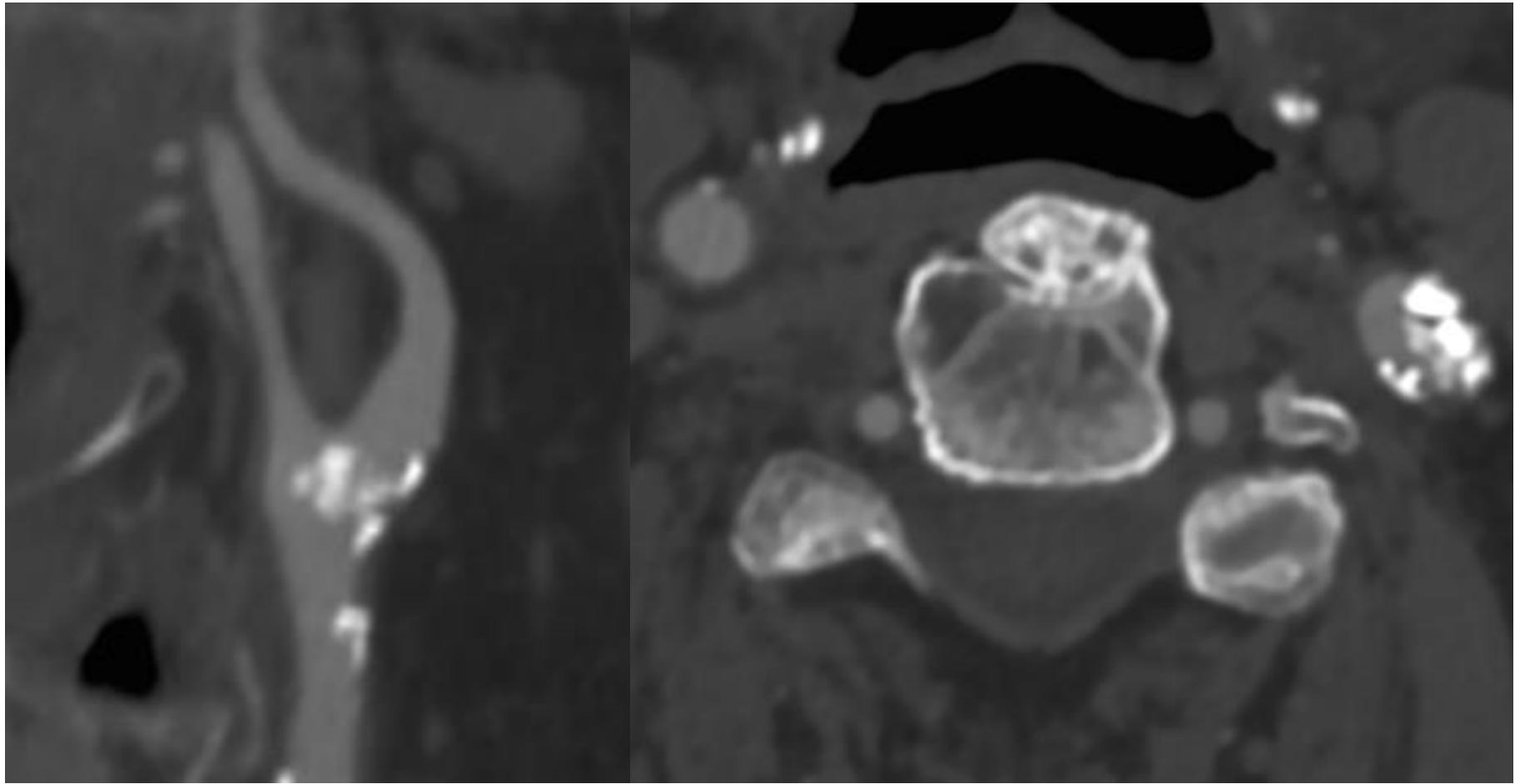
- $^{18}\text{F-NaF}$ = biomarqueur de l'hydroxyapatite et donc des calcifications osseuses et vasculaires
- Utilisé en pratique courante dans la détection / localisation des métastases osseuses
- Microcalcifications = processus inflammatoire → plaque vulnérable? (*Demer, Circulation 2008*)
- ≠ des macrocalcifications = phase finale du processus, visibles au scanner

Etude CARTIS en TEP/IRM, N. Noghossian – L. Mechtaouf, HCL – CERMÉP, Lyon

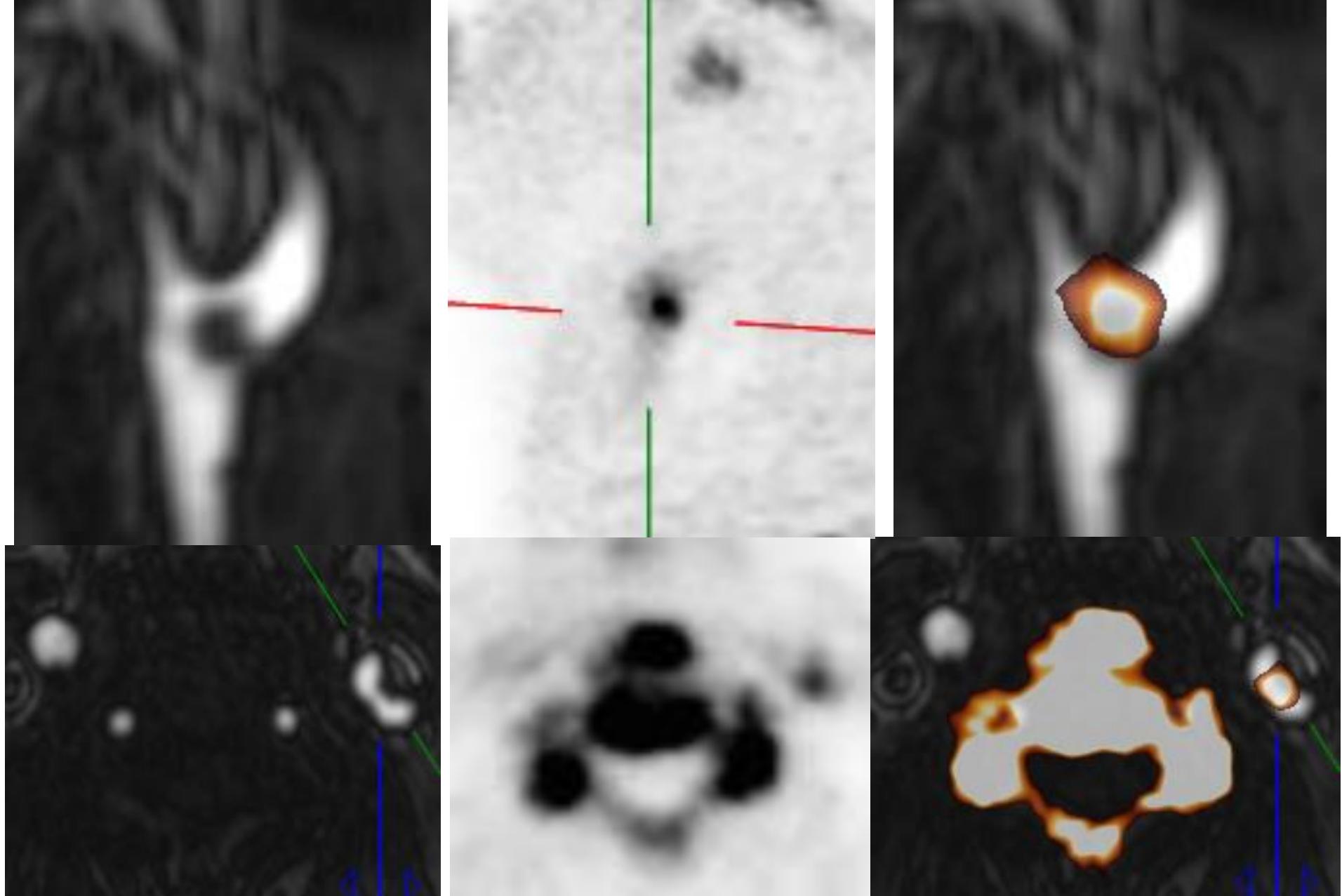


AngioCT TSA

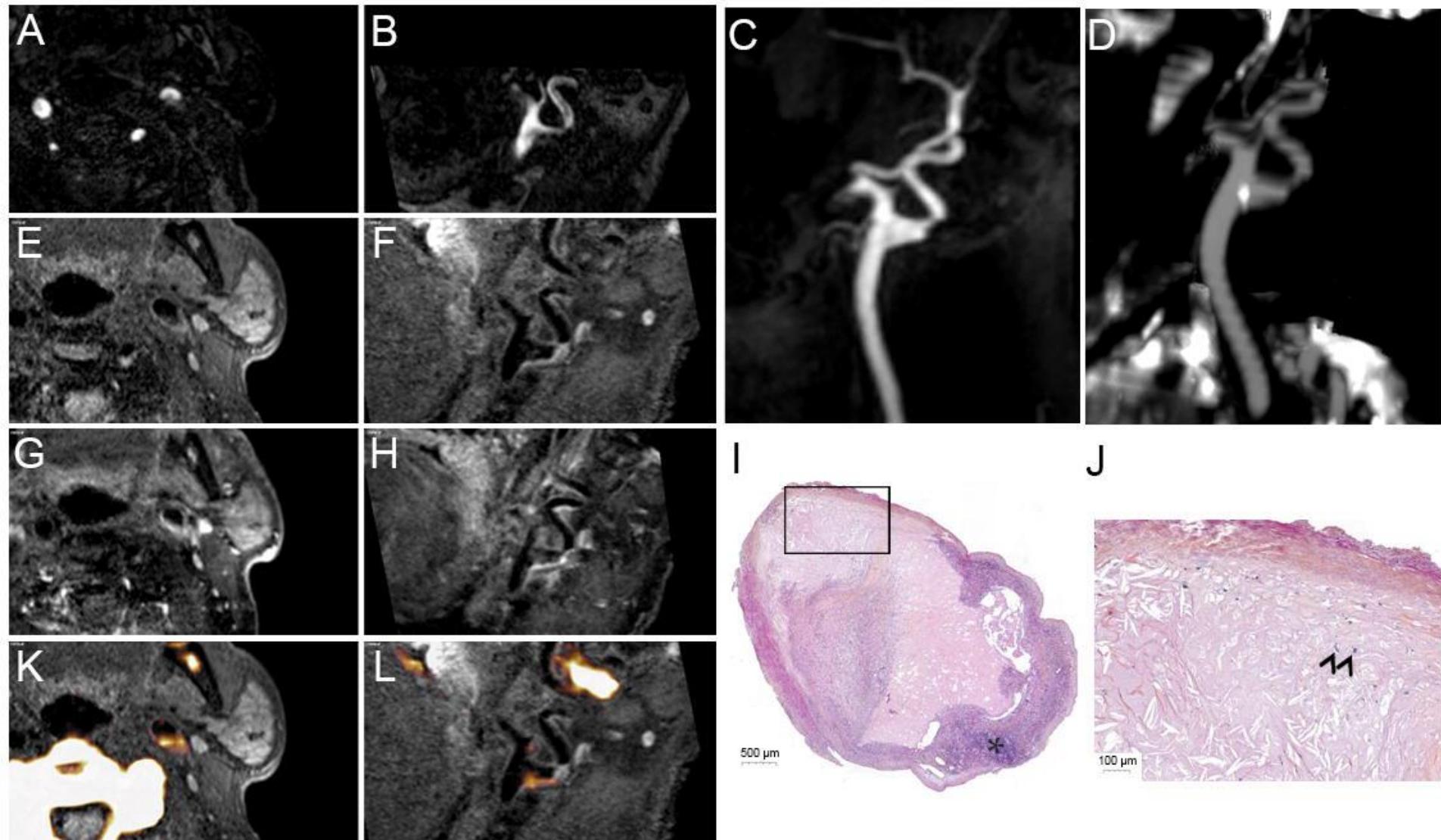
Plaque calcifiée
40-45% NASCET



Etude CARTIS en TEP/IRM, N. Nighoghossian – L. Mechtaouf, HCL – CERMÉP, Lyon



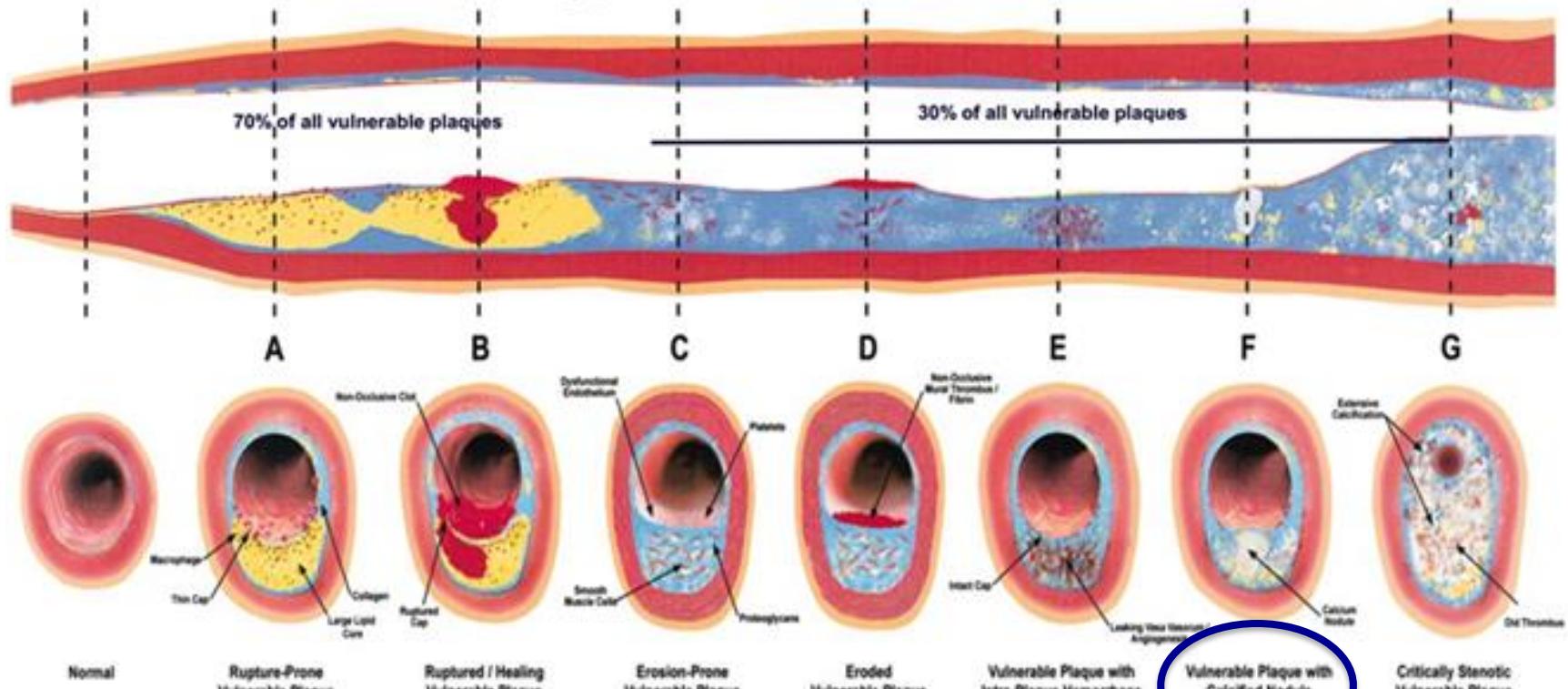
Etude CARTIS en TEP/IRM, N. Nighoghossian – L. Mechtouf, HCL – CERMEP, Lyon



Etude CARTIS en TEP/IRM, N. Nighoghossian – L. Mechtaouf, HCL – CERMÉP, Lyon

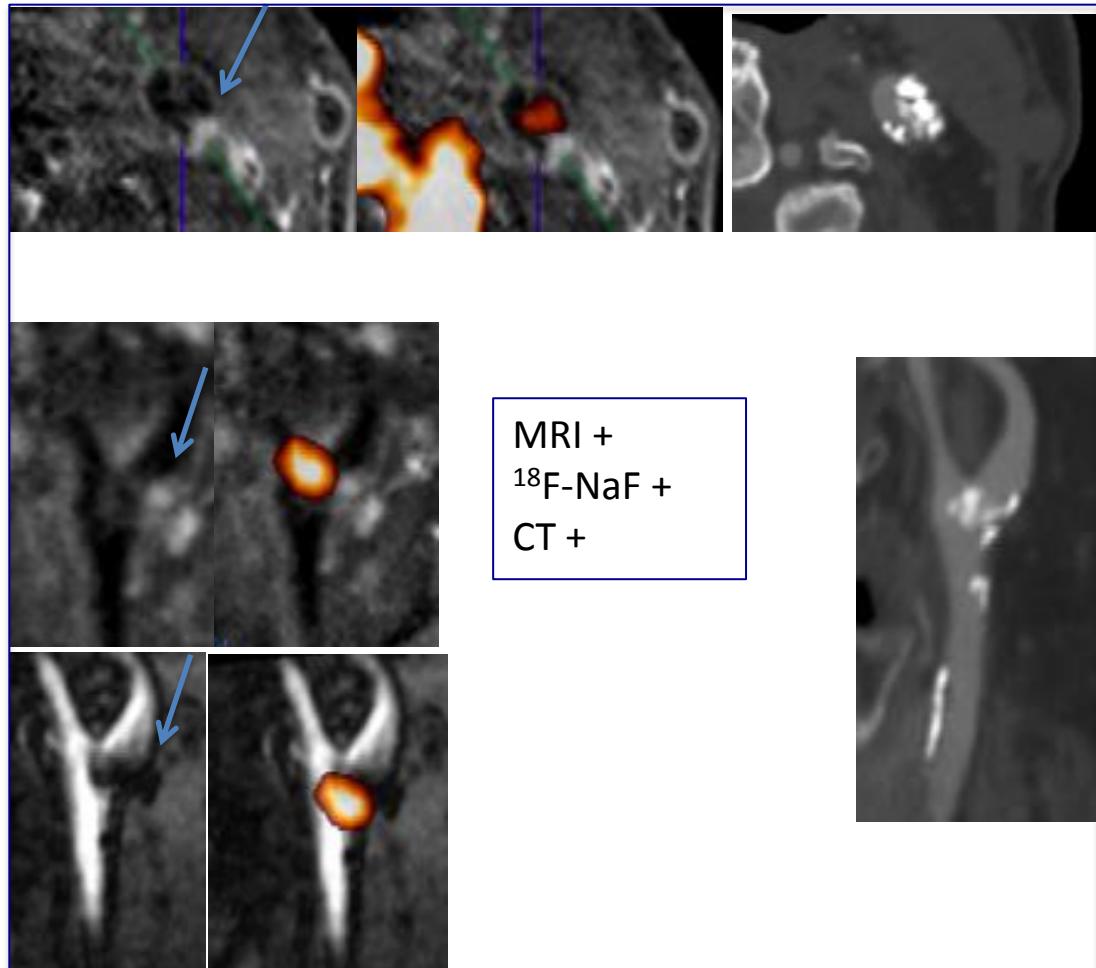
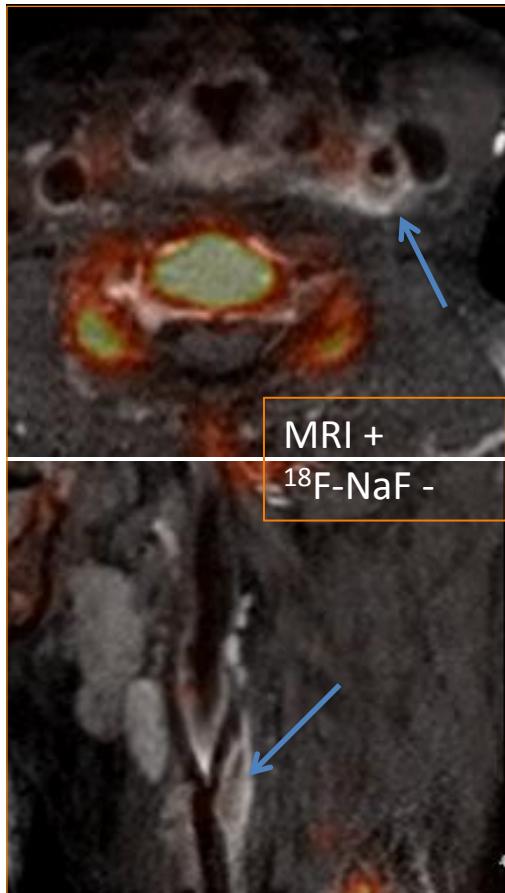


Different Types of Vulnerable Plaque





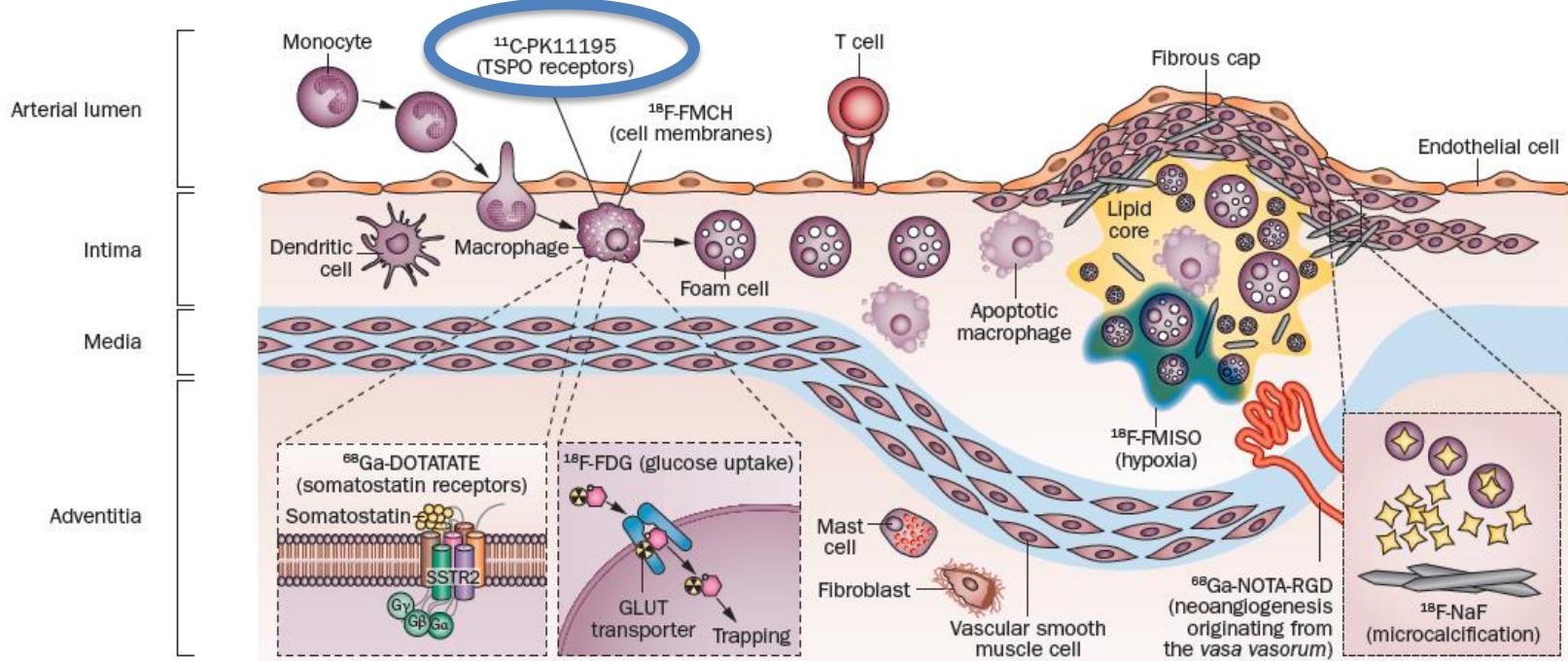
¹⁸F-NaF PET/MRI de phénotypes vulnérables différents



Etude CARTIS en TEP/IRM, N. Nighoghossian – L. Mechtaouf, HCL – CERMÉP, Lyon



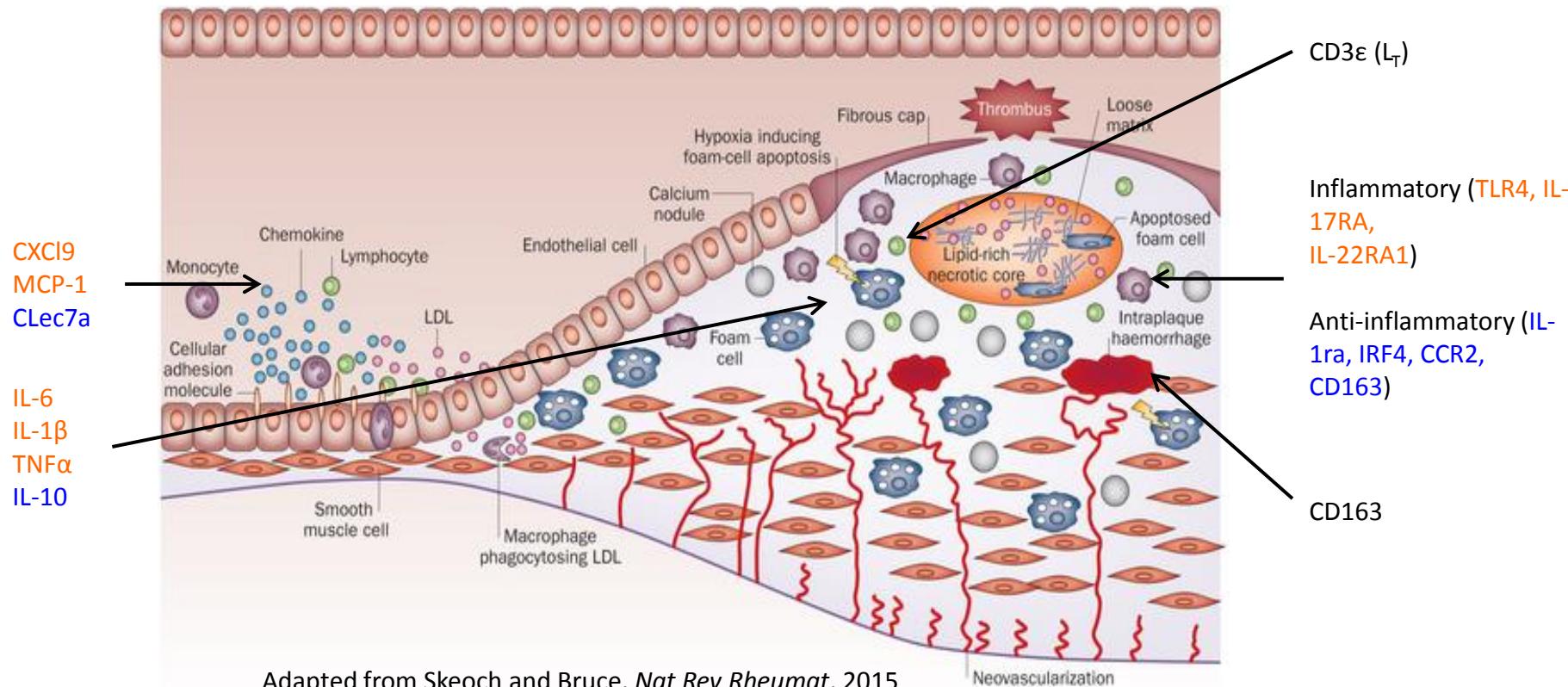
Les traceurs TEP de la plaque vulnérable



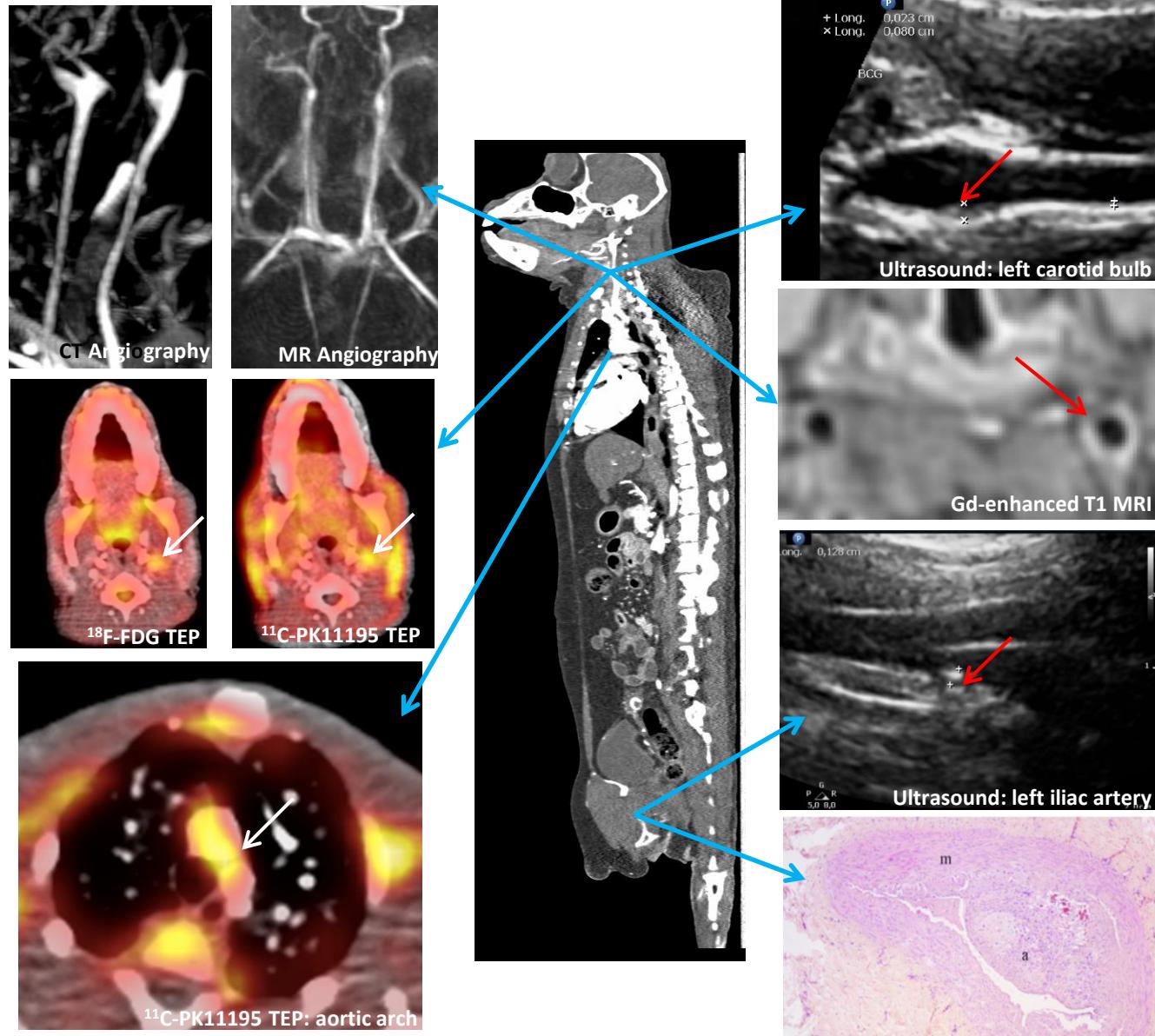
Tarkin JM, Joshi FR & Rudd JH, *Nature Rev Cardiol*, 2014

Etude translationnelle PET/IRM et génomique

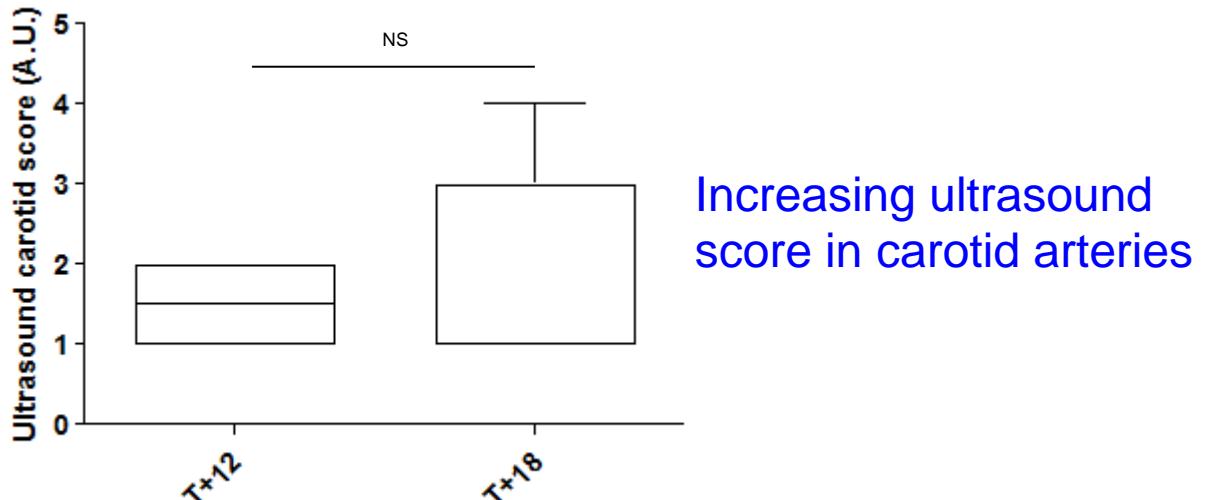
Tester une combinaison de biomarqueurs (imagerie et génomique) métaboliques, inflammatoires et anti-inflammatoires dans un modèle de primate non humain (PNH)



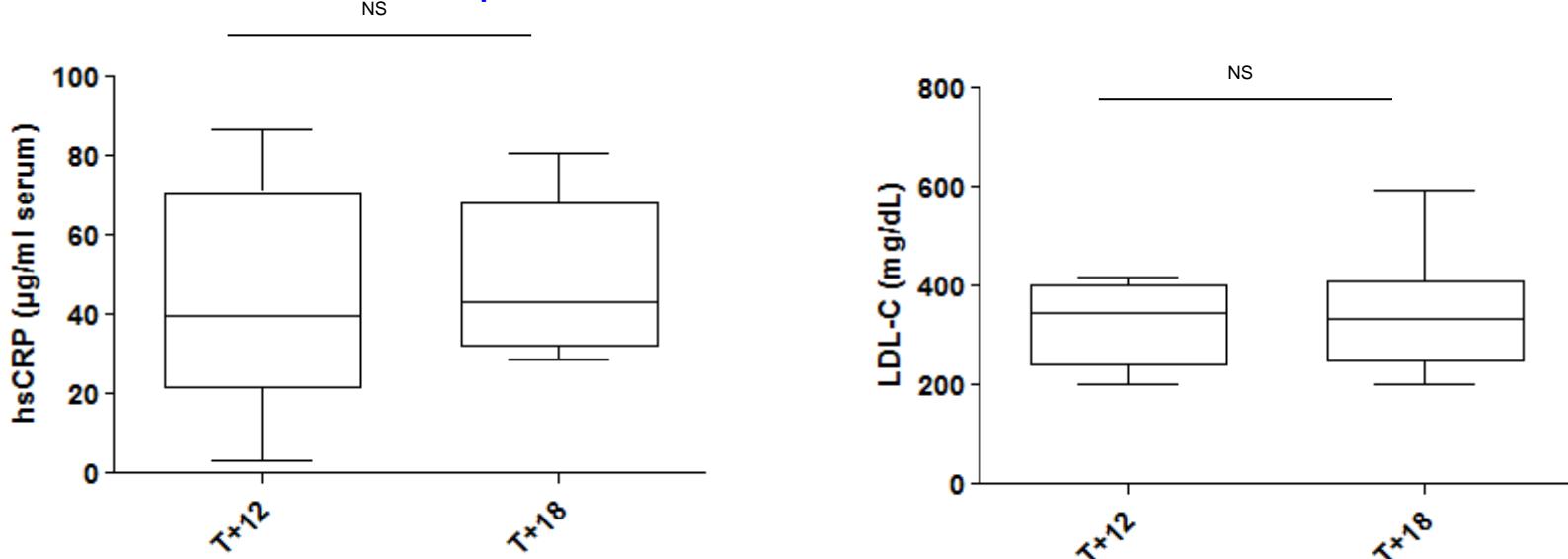
Lésions multi-sites avec des caractéristiques de plaque vulnérable



Evolution des lésions en échographie et marqueurs systémiques



Elevated hs-CRP and plasma LDL-C level at T+12 and T+18 months

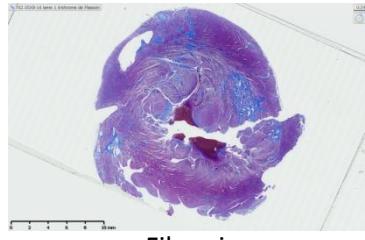
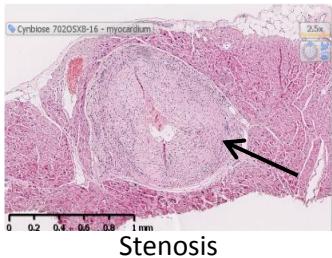


hsCRP in cynomolgus monkeys: basal ($0.6 - 1.5 \mu\text{g}/\text{ml}$) ; acute inflammation ($248 - 451 \mu\text{g}/\text{ml}$)



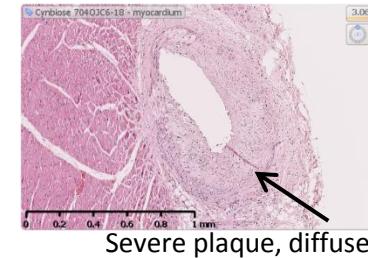
Trois sujets à risque avec des évènements cardio/cérébro-vasculaires

HC#9

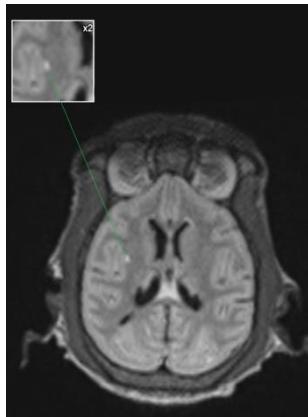
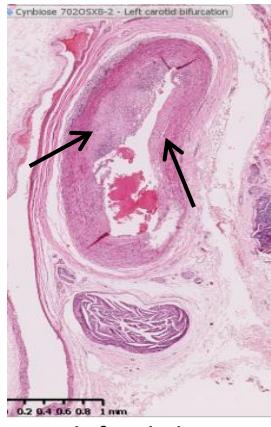


Coronary plaque and myocardial fibrosis

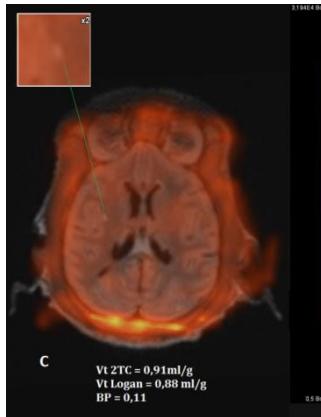
HC#13



Carotid plaque and cerebrovascular outcomes



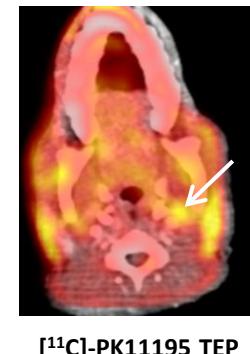
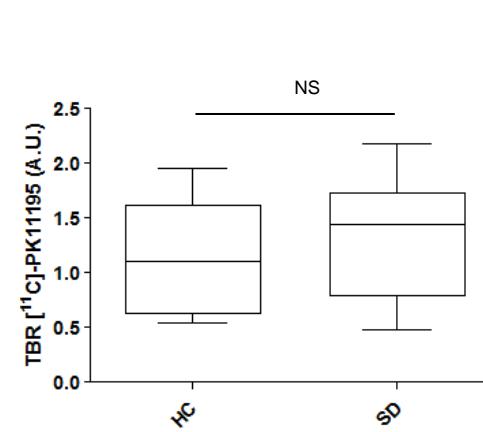
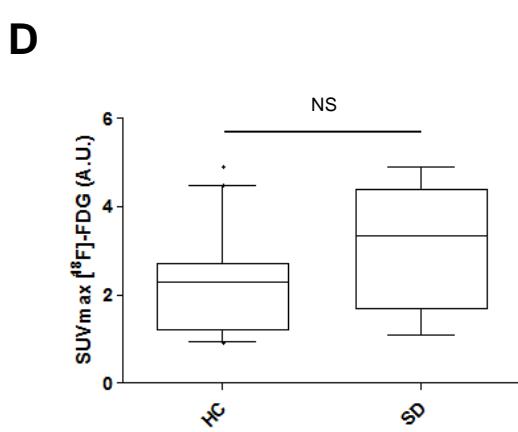
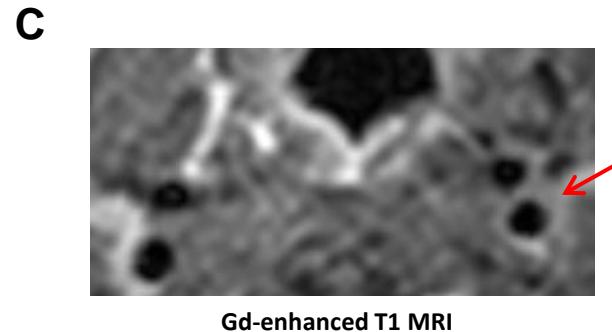
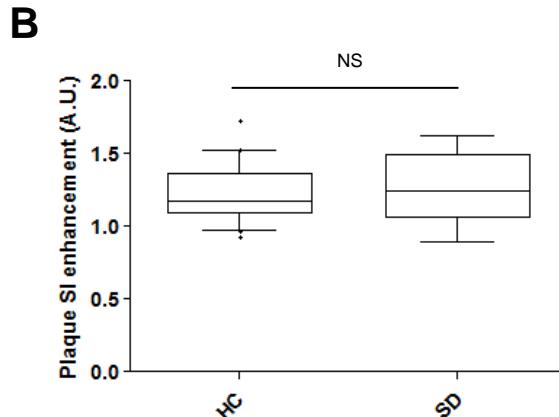
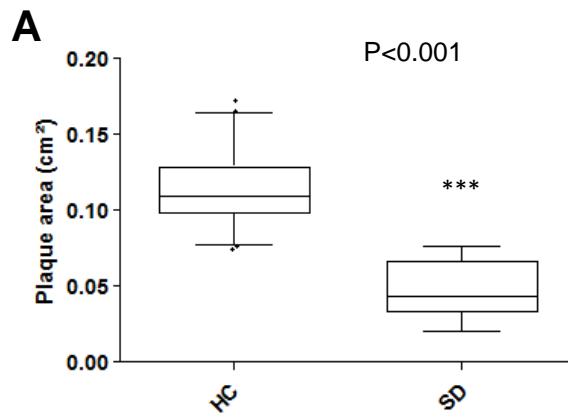
Lacunar stroke



Carotid thickening at the T+18 months ultrasound session (score>2)



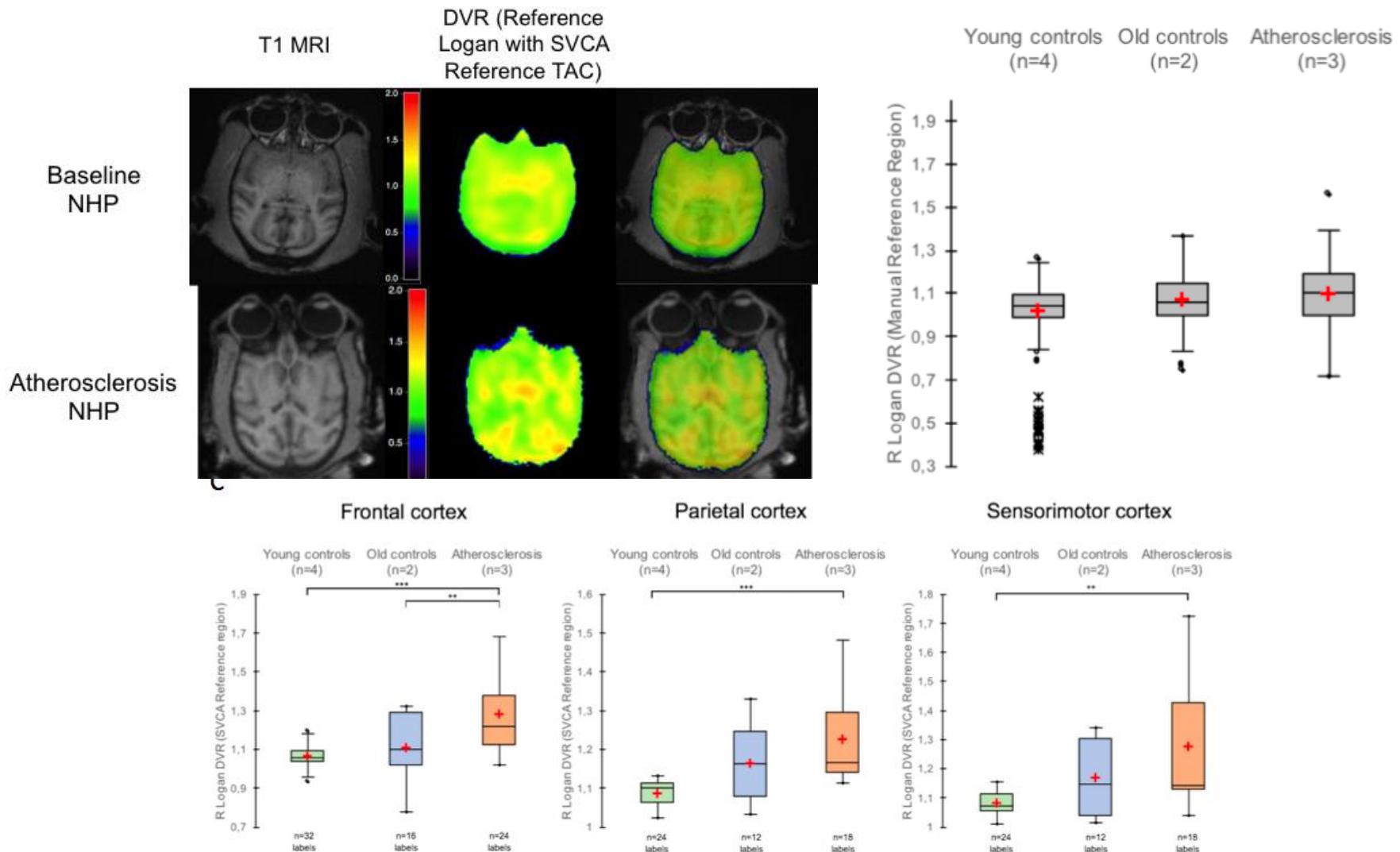
Inflammation métabolique périphérique dans les carotides



Correlation between metabolic and inflammatory PET tracers activity



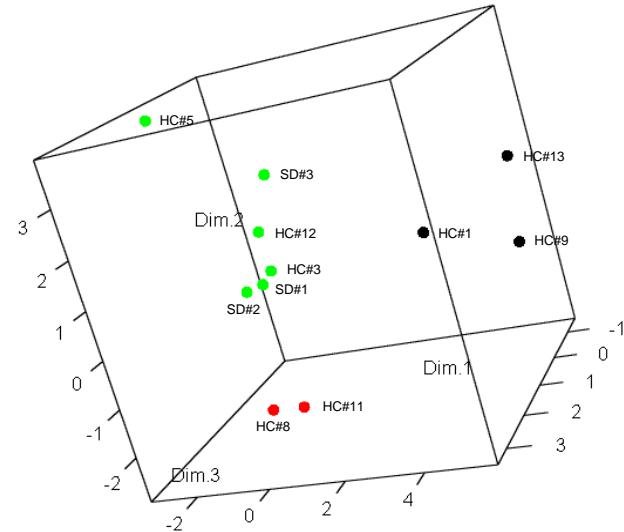
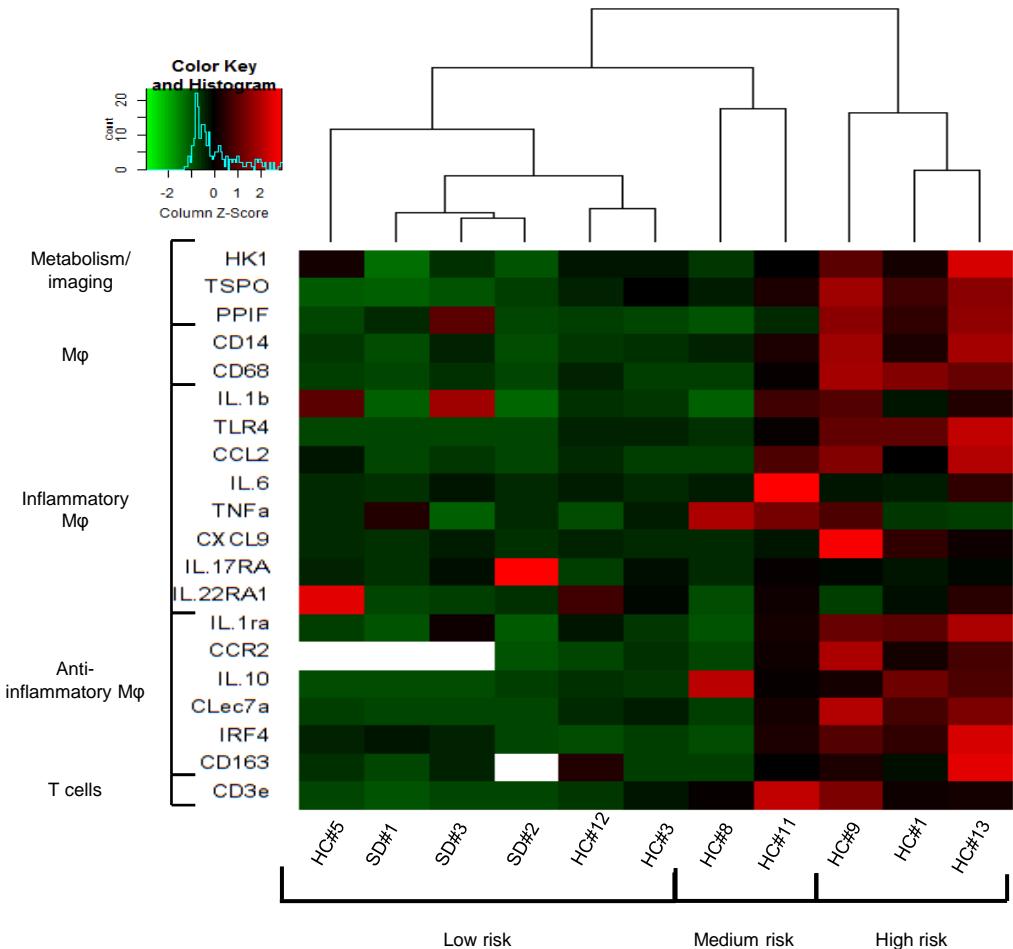
Inflammation métabolique centrale



Inflammation in cortex is associated with lower metabolic activity

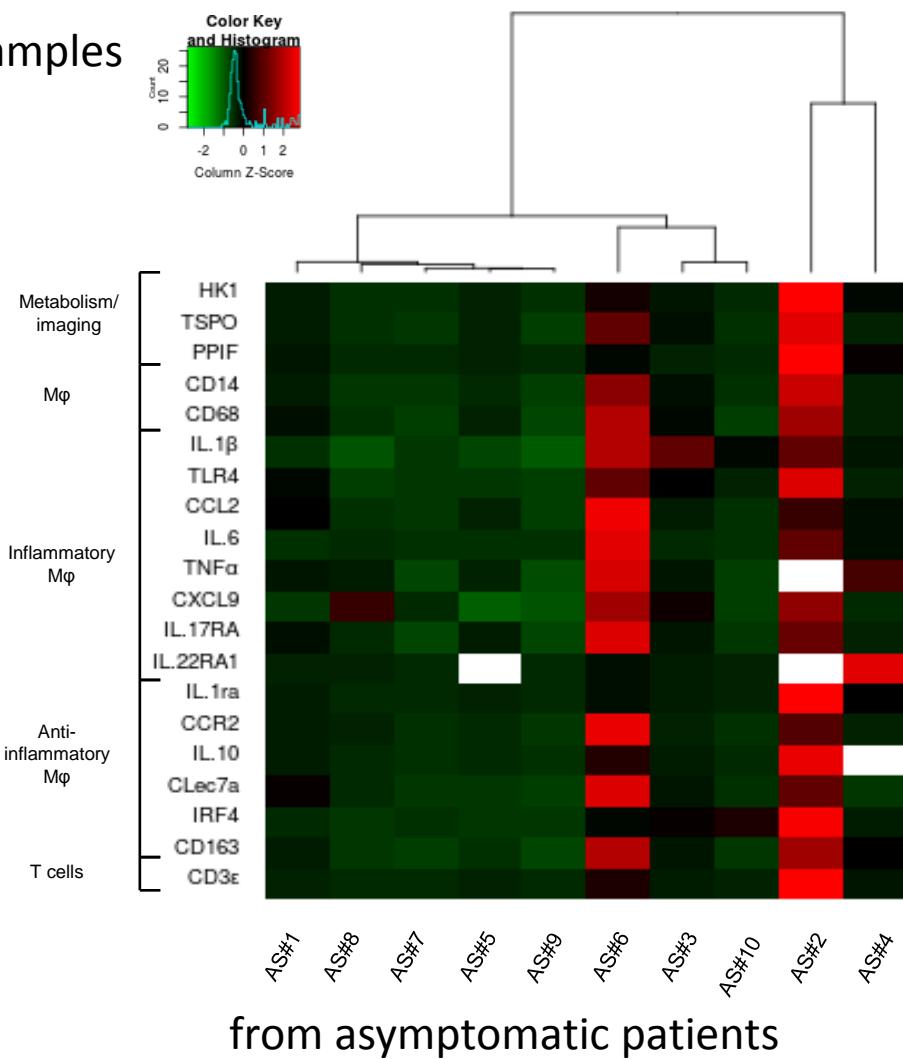
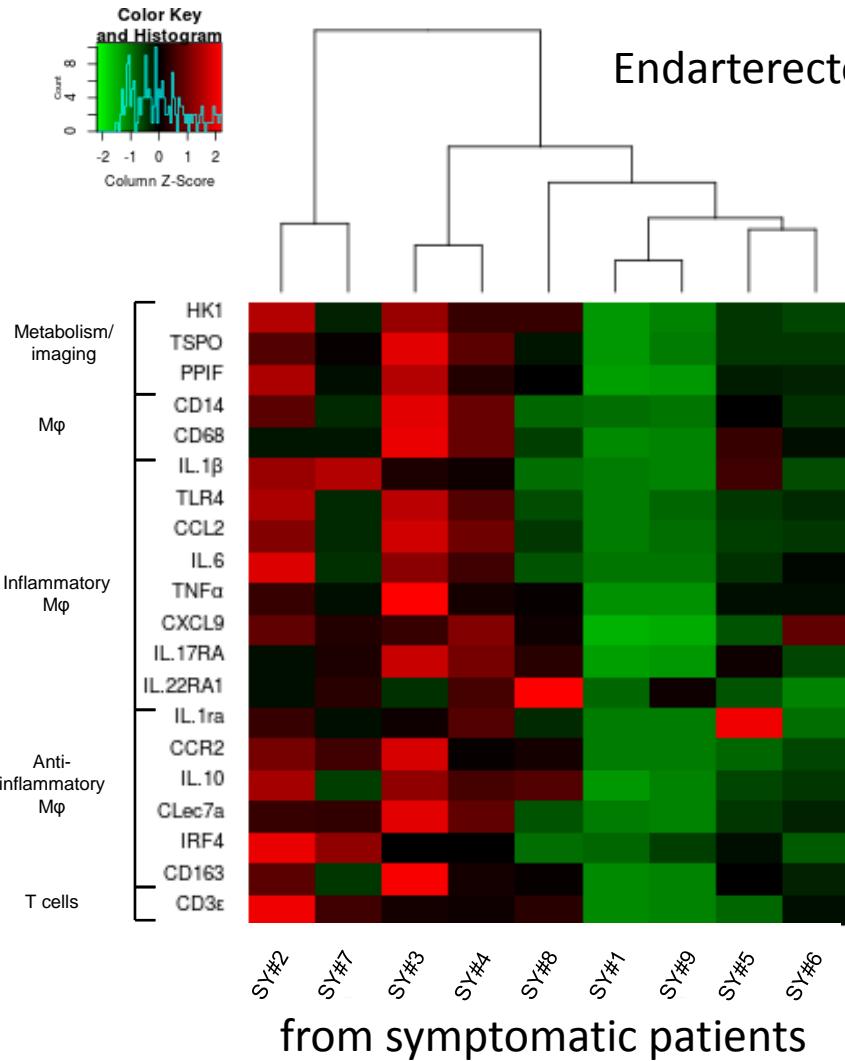


Marqueurs génomiques des plaques vulnérables



At-risk subjects have a similar profile
High expression of metabolic + inflammatory + anti-inflammatory genes

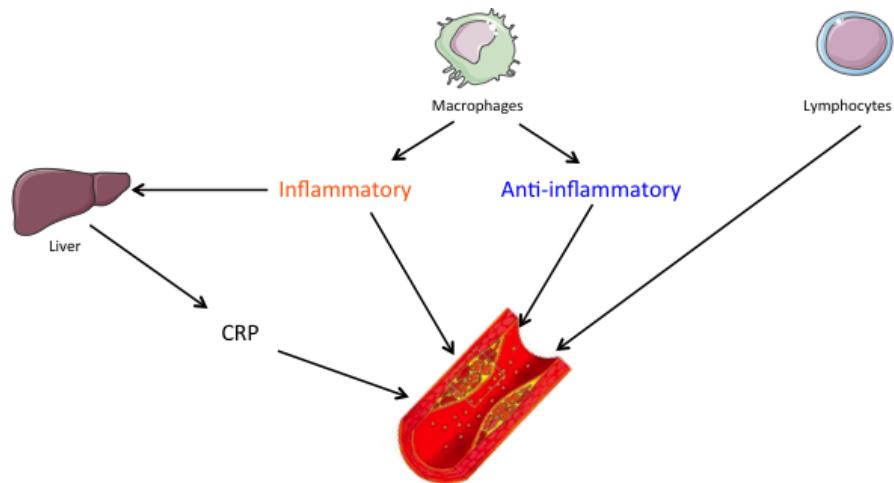
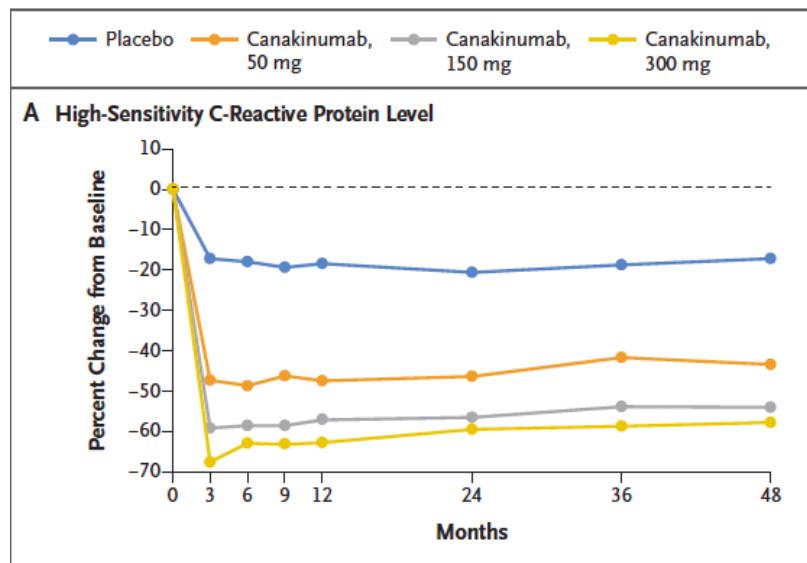
Marqueurs génomiques cliniques des plaques vulnérables



At-risk profile = High expression of metabolic + inflammatory + anti-inflammatory genes
More frequent in symptomatic / asymptomatic patients



Etude CANTOS : première étude positive d'un anti-inflammatoire (anti IL1-béta) sur le risque cardio-vasculaire

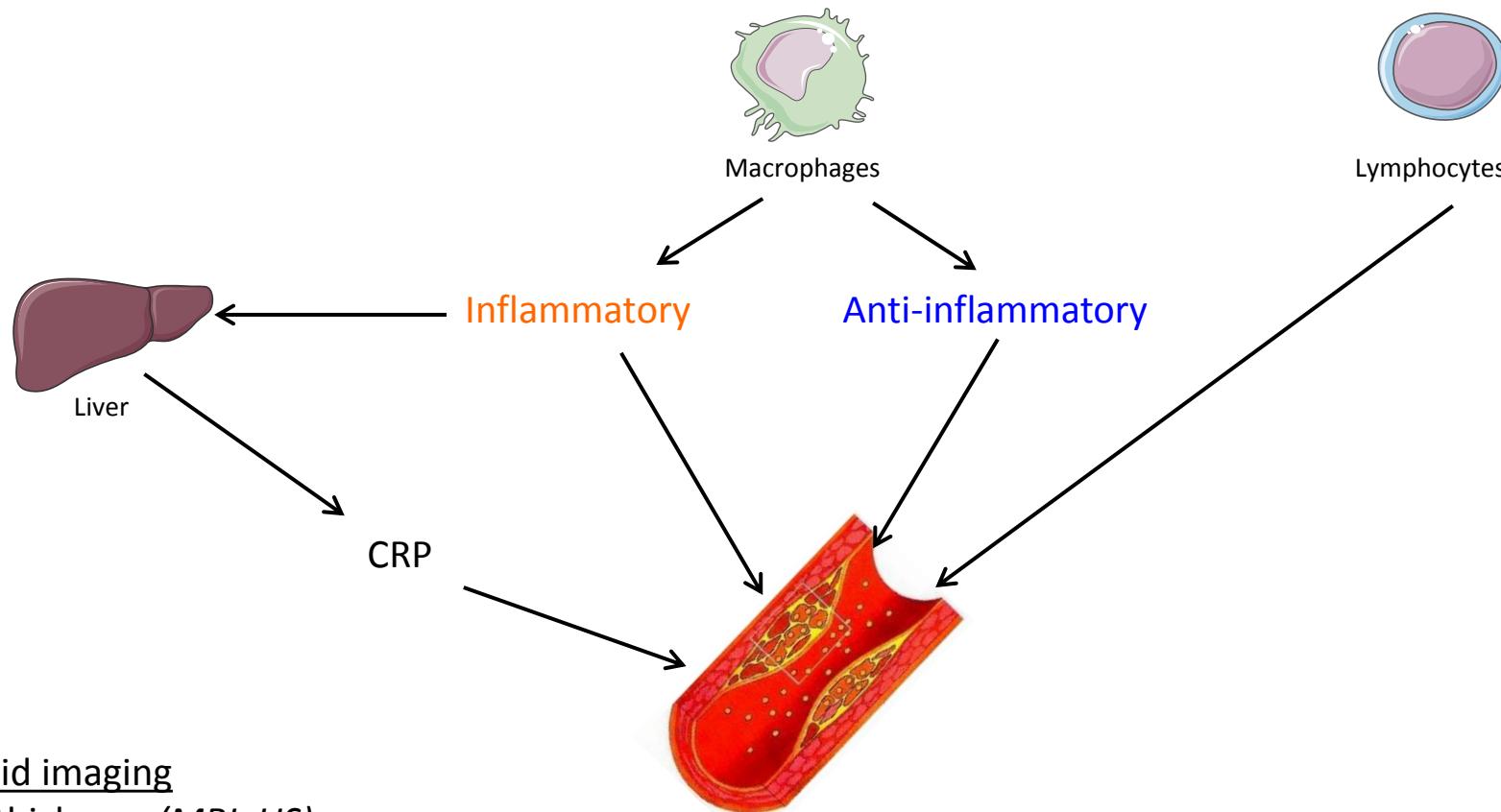


C-Reactive Protein
hs-CRP > 2 mg/L = 1st line biomarker

Ridker PM, NEJM 2017
Ridker PM, Lancet 2017



Vers une combinaison optimale de marqueurs d'inflammation et d'imagerie pour traiter le risque cardio-vasculaire



Carotid imaging

Wall thickness (MRI, US)

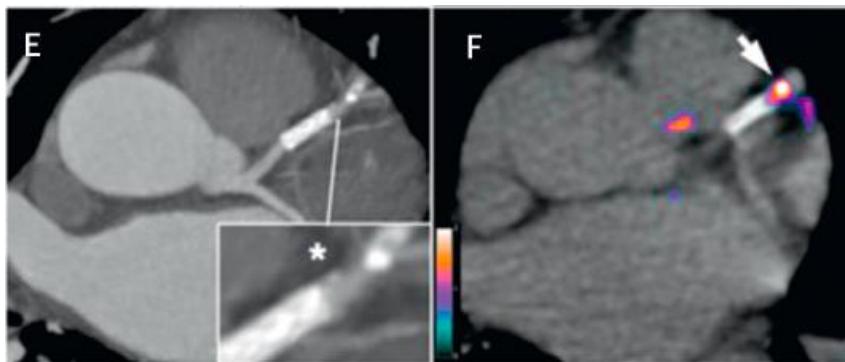
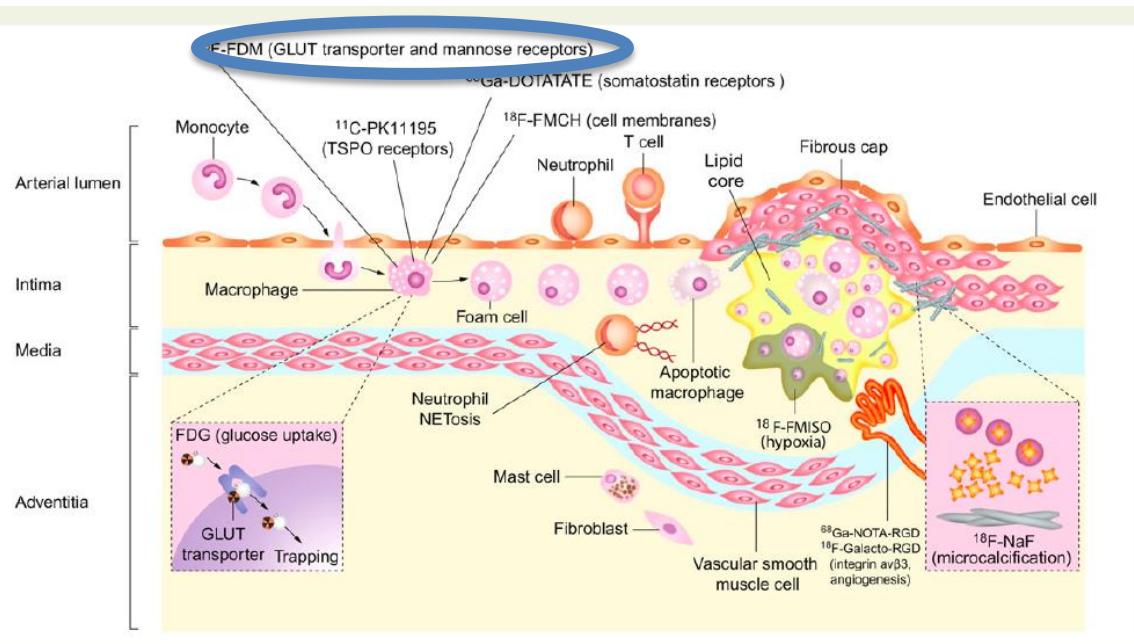
Metabolism (¹⁸F-FDG)

Inflammation/mitochondria activation (TSPO imaging)

Hyafil F et al. Eur J Nucl Med Mol Imaging 2016



Nouveaux traceurs TEP pour l'inflammation : ^{68}Ga -DOTATATE



Tarkin JM, JACC 2017

Tahara N, Nature Med 2014
Zanni MV, J Inf Dis, 2017



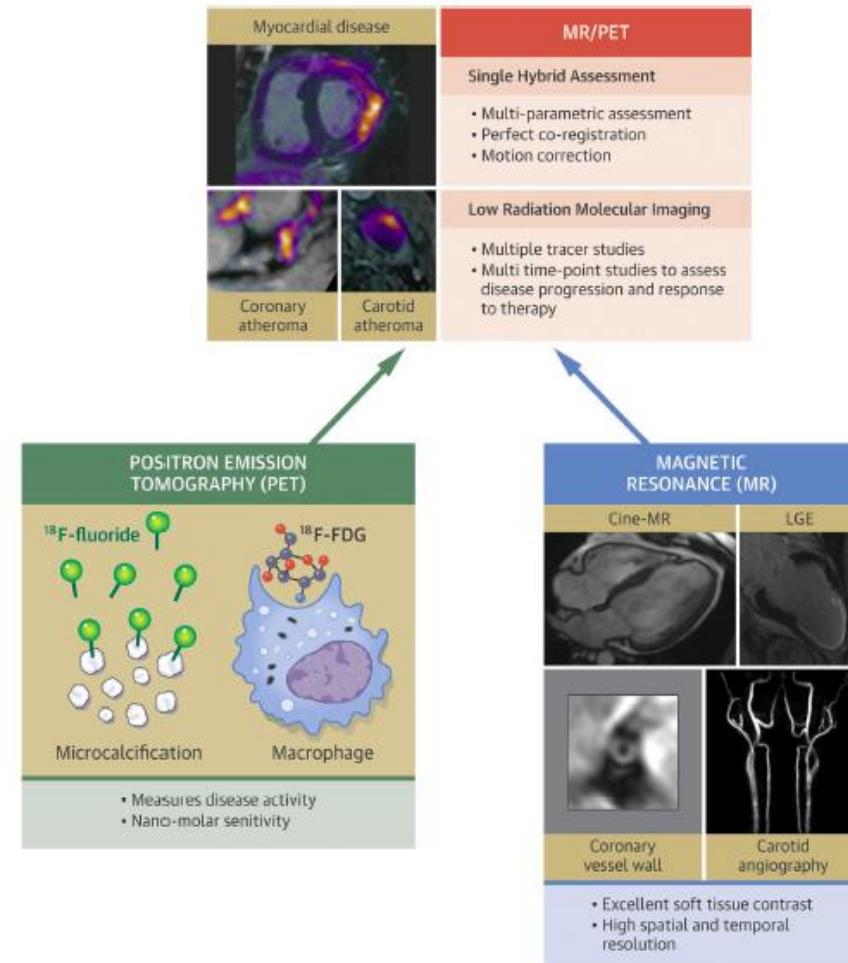
Conclusion - Perspectives

- Inflammation = nouvelle cible thérapeutique de l'athérosclérose
- hsCRP = le premier biomarqueur clinique
- TEP/IRM ou TEP/CT = examen des nouveaux traitements ?

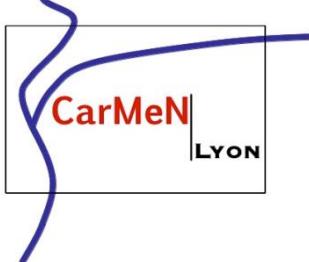
Examens TEP hybrides avec le radiotraceur clinique du site

- NaF + TEP/CT coronaire et cœur
- FDG ou traceur TSPO + TEP/IRM carotides et cerveau

Un nouveau traceur combinant tous les avantages?



Robson, P.M. et al. J Am Coll Cardiol Img. 2017



DI CATALDO V.
GELOEN A.
PAILLARD M.
WIART M.
AUGEUL L.
DEBATISSE J.
OVIZE M.
VIDAL H.

Creatis

NIGHOGHOSSIAN N.
MECHTOUFF L.
SIGOVAN M.



cynbiose
CLAVEL M.
CONTAMIN H.
VERSET M.
WATEAU O.
PATURET A.
TABORIK F.

SIEMENS
Healthineers

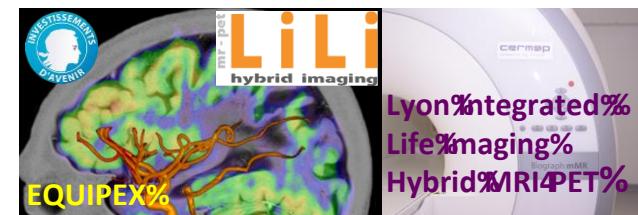
TROALEN T.
DEBATISSE J.



Inserm

cermap
imagerie du vivant

IBAROLLA D.
COSTES N.
LAVENNE F.
LAMBERTON F.
PIRAQUIVE J.
LEBARS D.

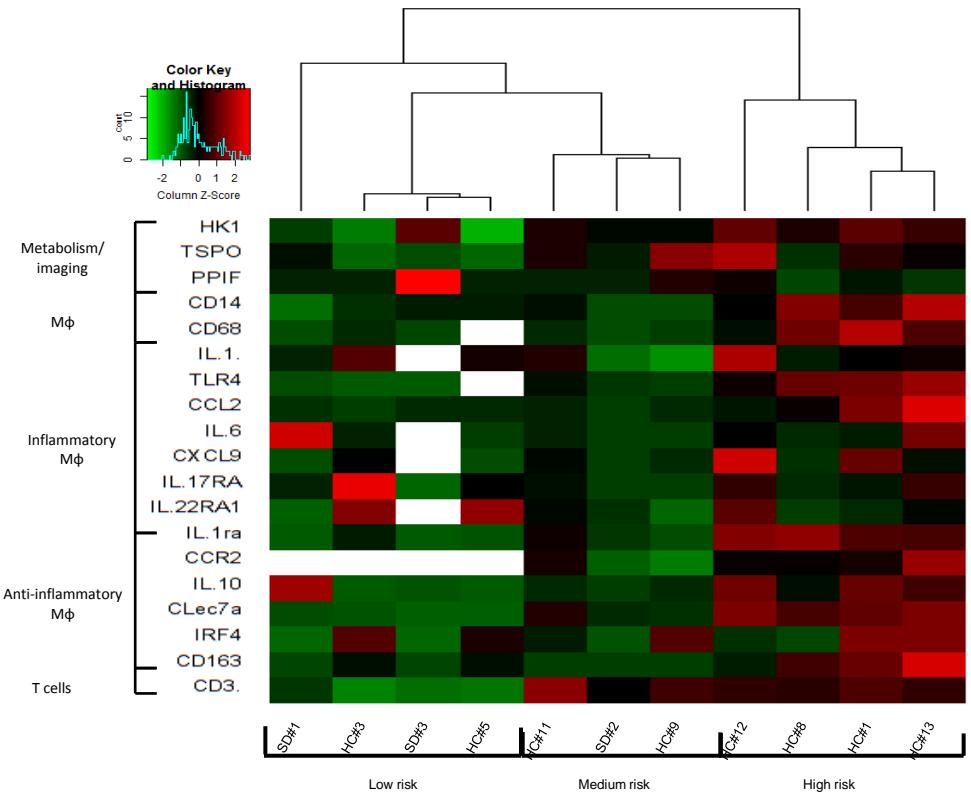


CYCLOPS, ANR-15-CE17-0020

Marvelous
New MR imAgeing to pRevent cErebral and myOcardial reperfUSSION injury

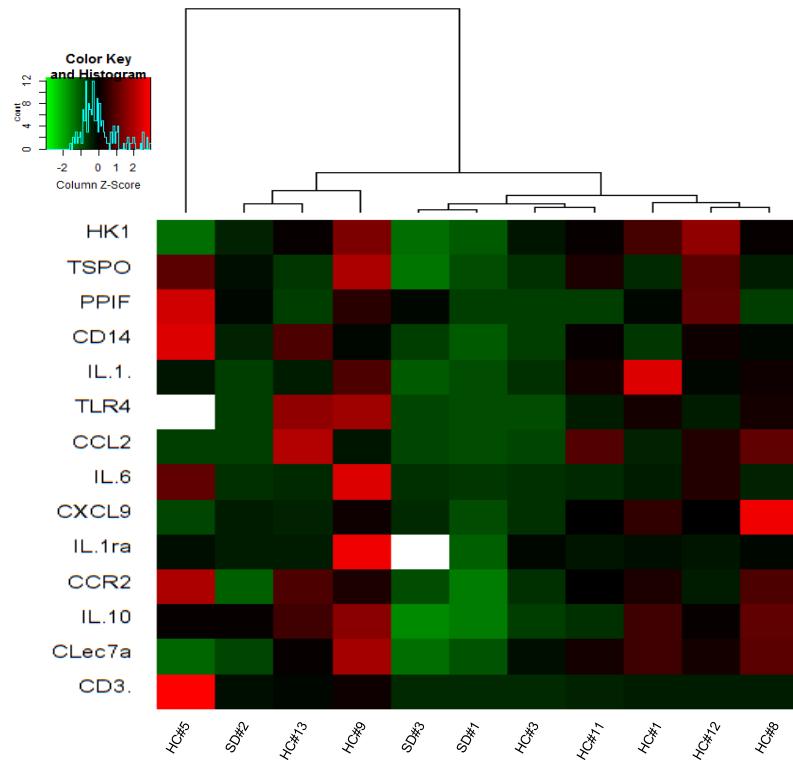


UNIVERSITÉ DE LYON
Université de Lyon



Aortic arch

Correlated with		r	p	Correlated with		r	p
Ccl2	Cd14	0.95	<0.001	Il-1β	Hk1 *	0.82	0.002
	Cd68	0.82	0.002		Tspo *	0.72	0.012
	Tlr4	0.95	<0.001		Il-1ra **	0.78	0.005
	Clec7a	0.79	0.004		Clec7a	0.76	0.007
	Cd163 **	0.92	<0.001		Il-17ra	0.85	<0.001
	Irif4 **	0.87	<0.001		Cd14	0.66	0.027
	Hk1 *	0.65	0.03		Cxcl9	0.63	0.038
	Il-1ra **	0.64	0.034		Ccr2	0.67	0.024
	Ccr2	0.67	0.024		Il-10 **	0.64	0.034
	Cd3ε	0.61	0.046		Cd3ε	0.74	0.009
		Il-6	Il-10 **			0.77	0.006



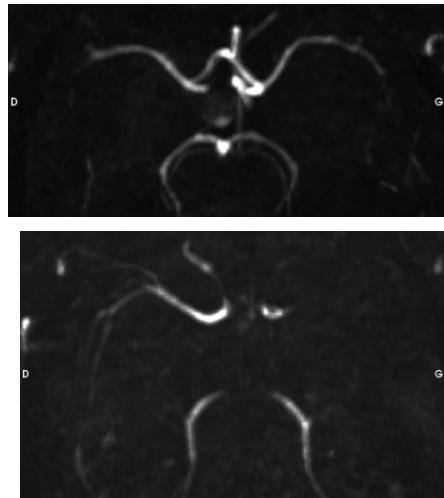
Abdominal aorta

Correlated with		r	p
Ccl2	Hk1 *	0.65	0.03
	Tlr4	0.72	0.012
	Ccr2	0.68	0.021
	Cd14	0.78	0.005
	Il-10 **	0.87	<0.001
	Clec7a	0.8	0.003
	Cd3ε	0.92	<0.001
Il-1β	Tspo *	0.64	0.034
	Il-6	0.93	<0.001
	Cd14	0.75	0.008
	Clec7a	0.63	0.038
Il-6	Cd14	0.68	0.021

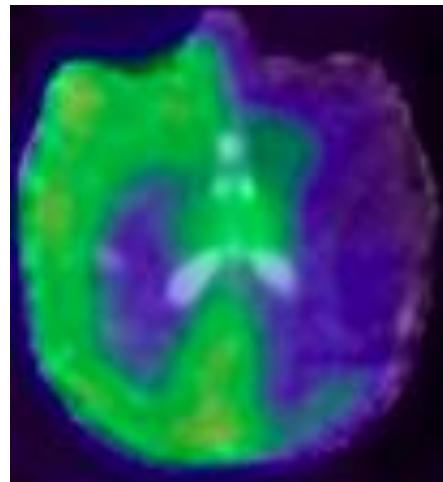
Endovascular stroke model



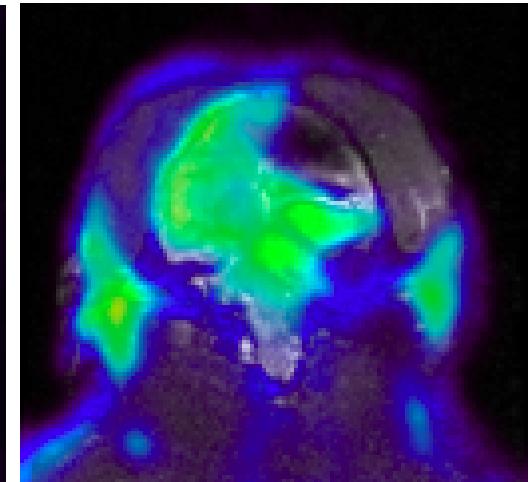
Angiography



MR Angiography



PET Perfusion



MRI

PET ($H_2^{15}O$) / MRI

First PET/MRI NPs for BBB damage in an endovascular NHP stroke model

Fast and easy generator radio-labelling

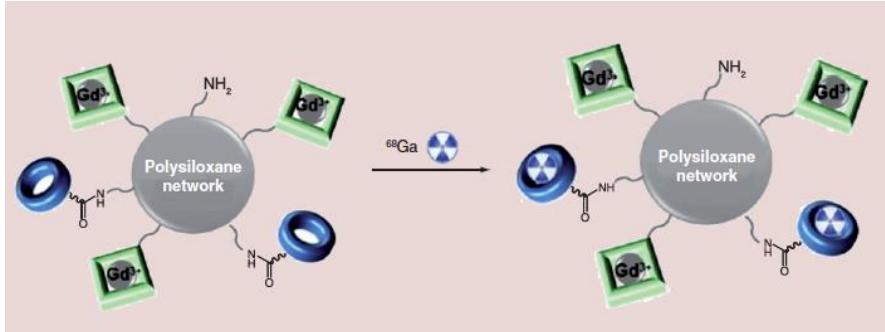
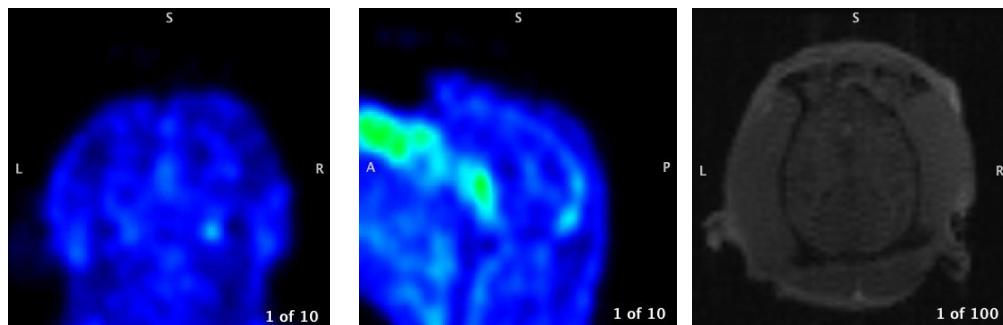
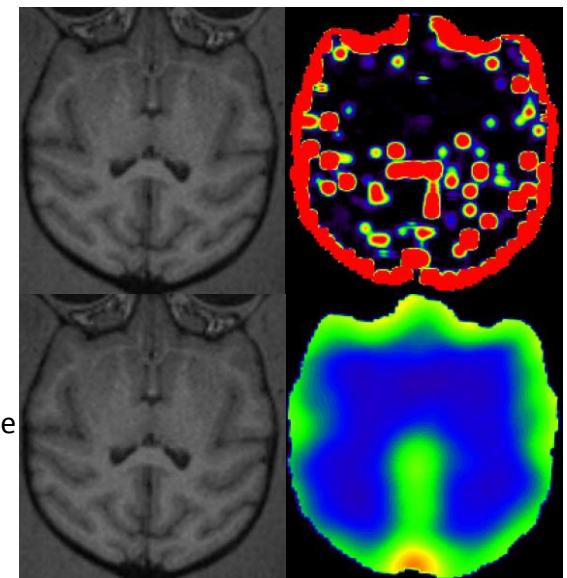


Table-top ^{68}Ga generator

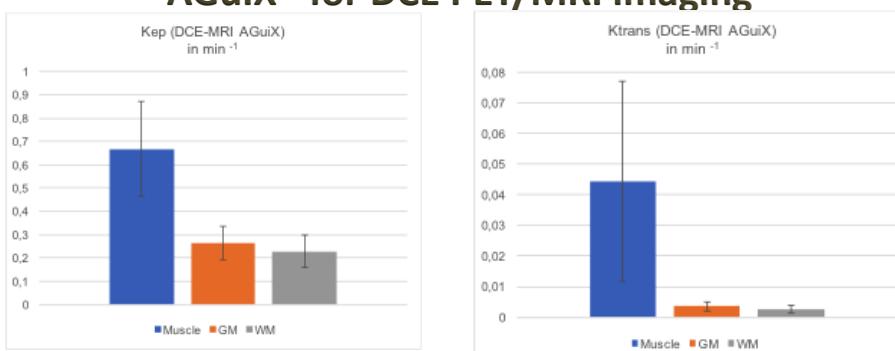


(Ktrans) DCE-
MRI

Gallium PET
Averaged frame

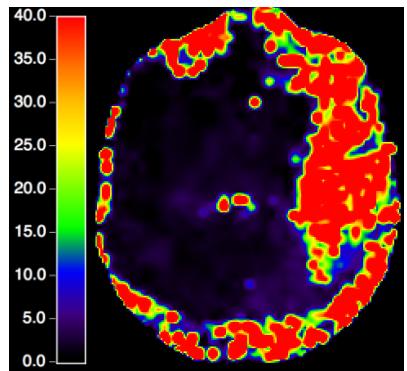


Sensitive and quantitative imaging
of permeability over time in stroke



Prediction of evolution and treatment decision

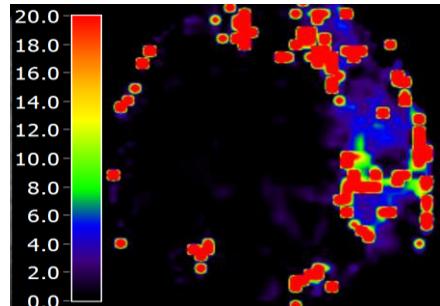
Tmax



ADC



- Large lesion with no penumbra
(100% risk of premature death)



- Medium size lesion at occlusion
(duration of occlusion monitored
by ADC growth)
 - Blinded CsA trial