




# Imagerie nucléaire des plaques d'athérome vulnérables.

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**2<sup>ème</sup> Congrès : Journées francophones de Médecine Nucléaire**  
**Samedi 21 mai 2016**  
**Grenoble**

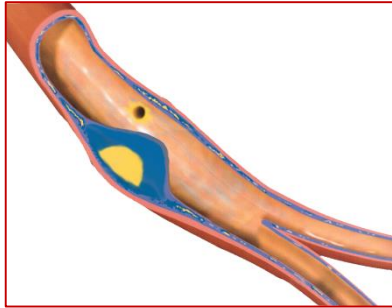
# La maladie coronaire

1/3

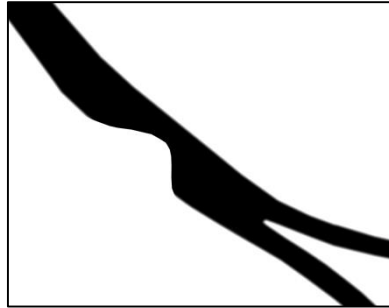
CAD en pratique clinique

2/3

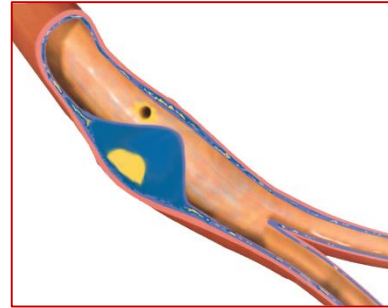
stable



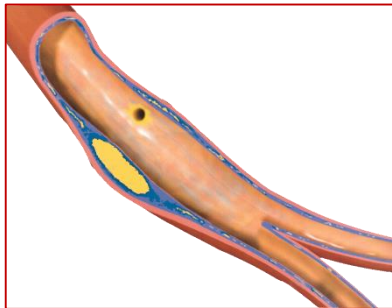
angiographie



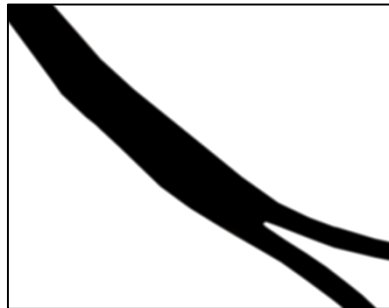
stenose



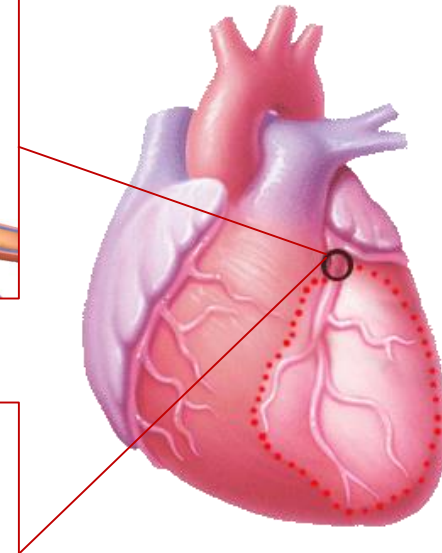
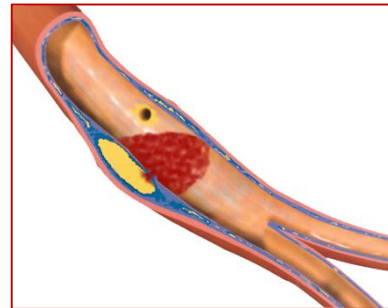
vulnérable



angiographie



rupture

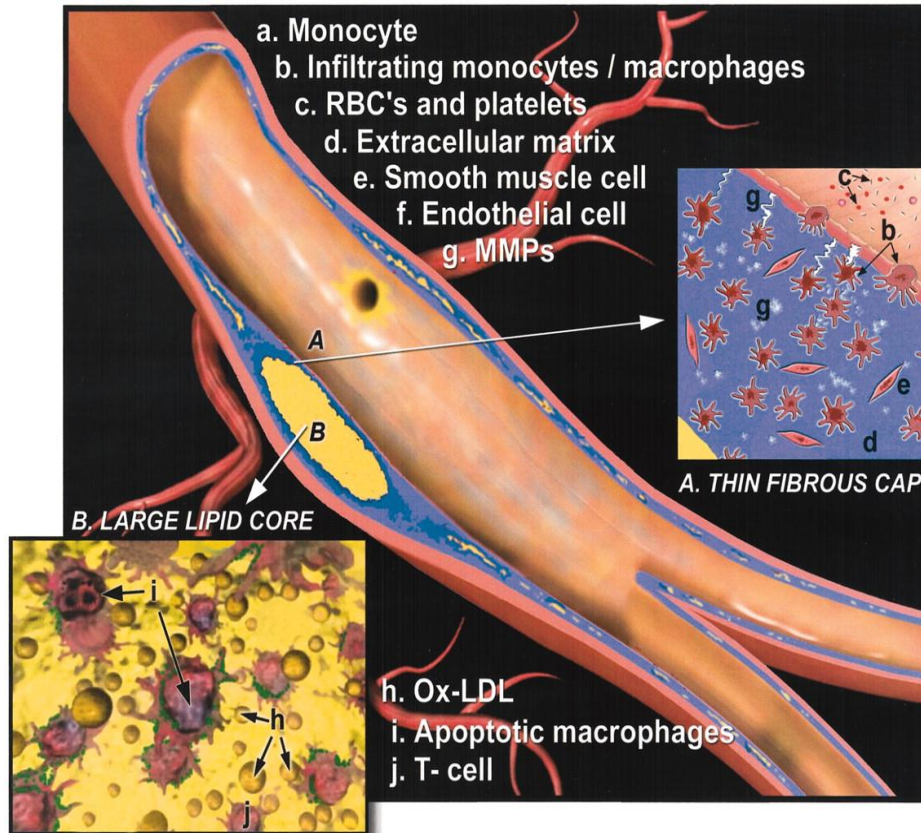


⇒ Ischémie

⇒ Infarctus

⇒ Besoin clinique: diagnostiquer les plaques vulnérables

# Comment discriminer les plaques vulnérables?



Naghavi, Circulation 2003

**TABLE 4. Criteria for Defining Vulnerable Plaque, Based on the Study of Culprit Plaques**

**Major criteria**

- Active inflammation (monocyte/macrophage and sometimes T-cell infiltration)
- Thin cap with large lipid core
- Endothelial denudation with superficial platelet aggregation
- Fissured plaque
- Stenosis >90%

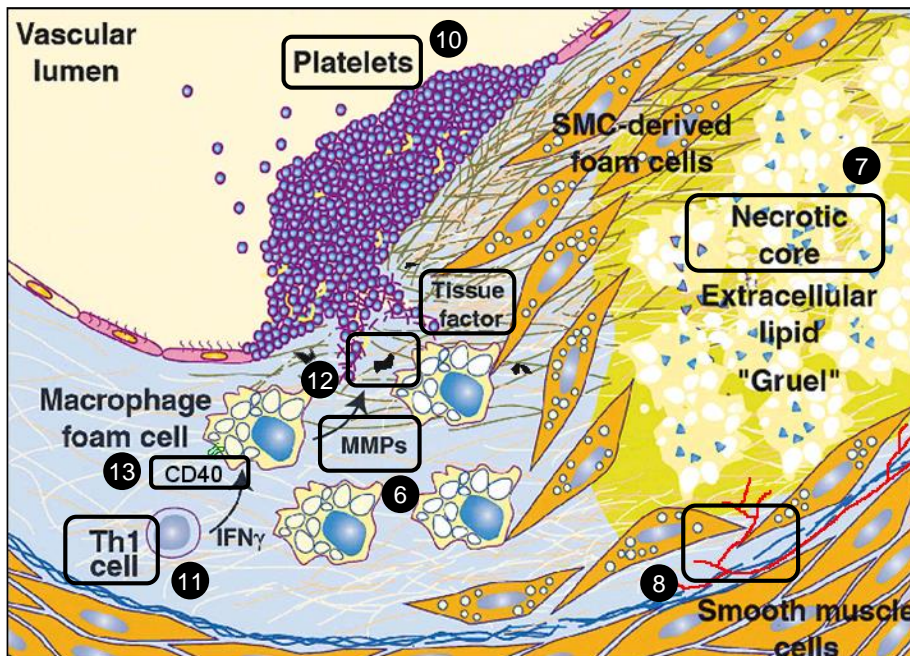
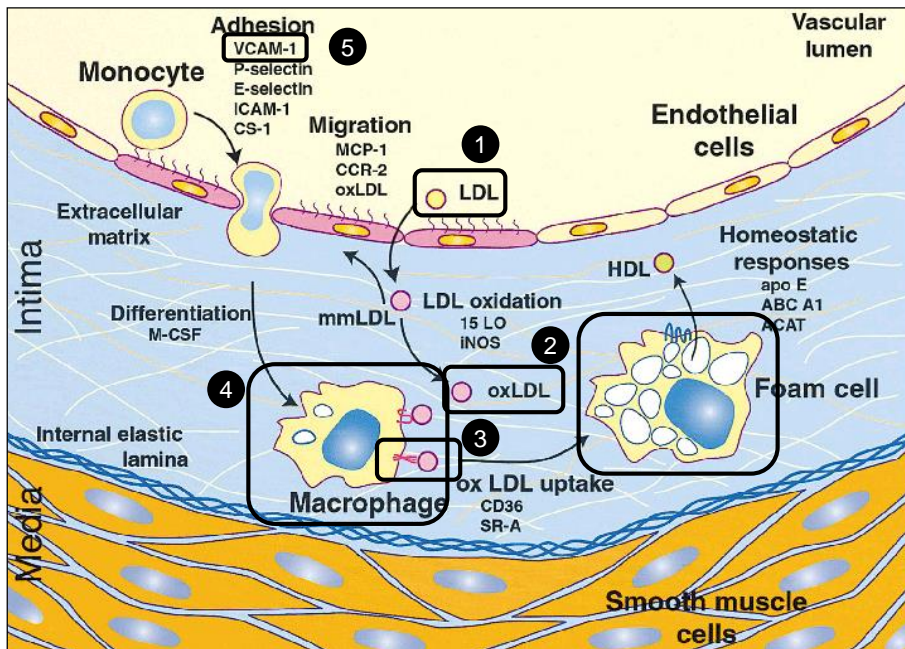
**Minor criteria**

- Superficial calcified nodule
- Glistening yellow
- Intraplaque hemorrhage
- Endothelial dysfunction
- Outward (positive) remodeling

# Le challenge de l'imagerie des plaques vulnérables.

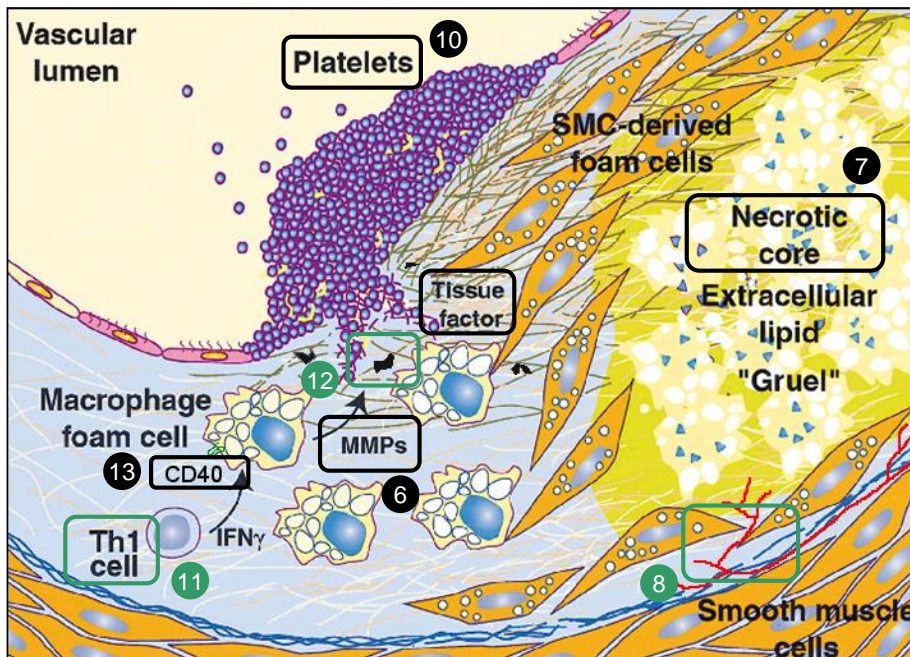
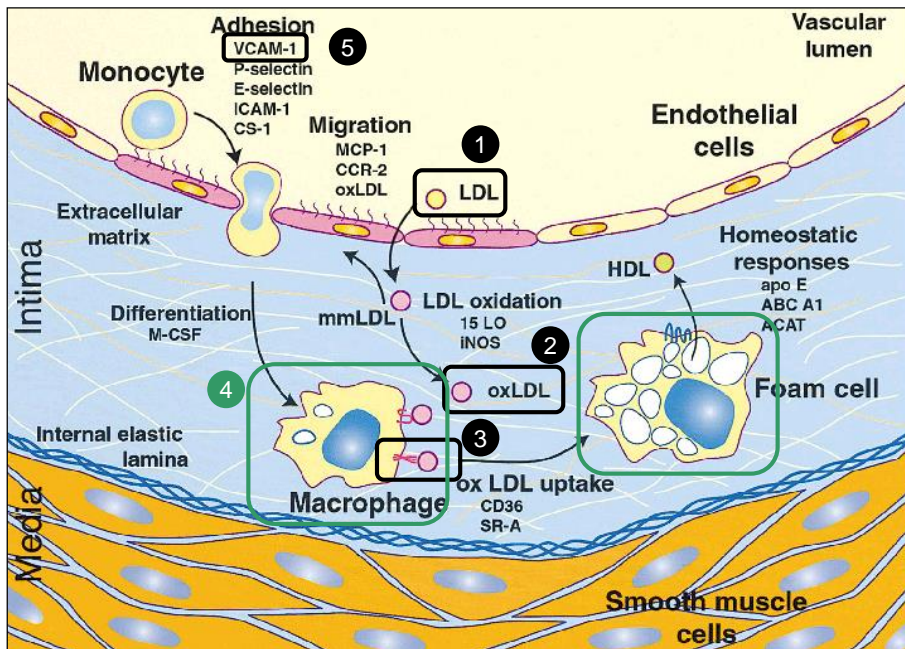
- Faible volume des lésions
- Mouvements cardiaques et respiratoires
- Absence de modèles animaux de rupture
- La cinétique d'évolution des plaques est mal connue
- Requière de larges cohortes et un long suivie

# Evalués sur des modèles animaux



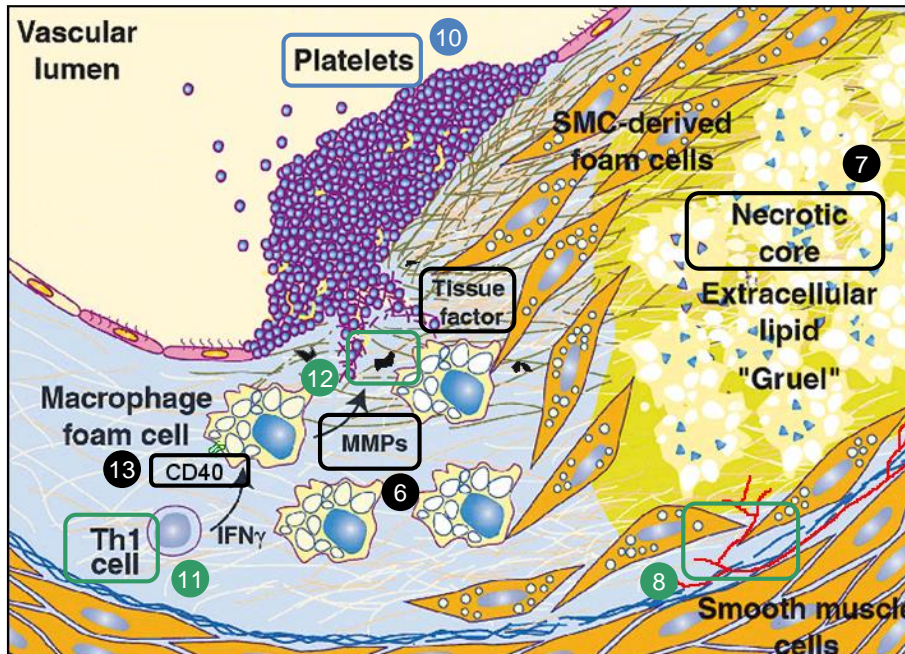
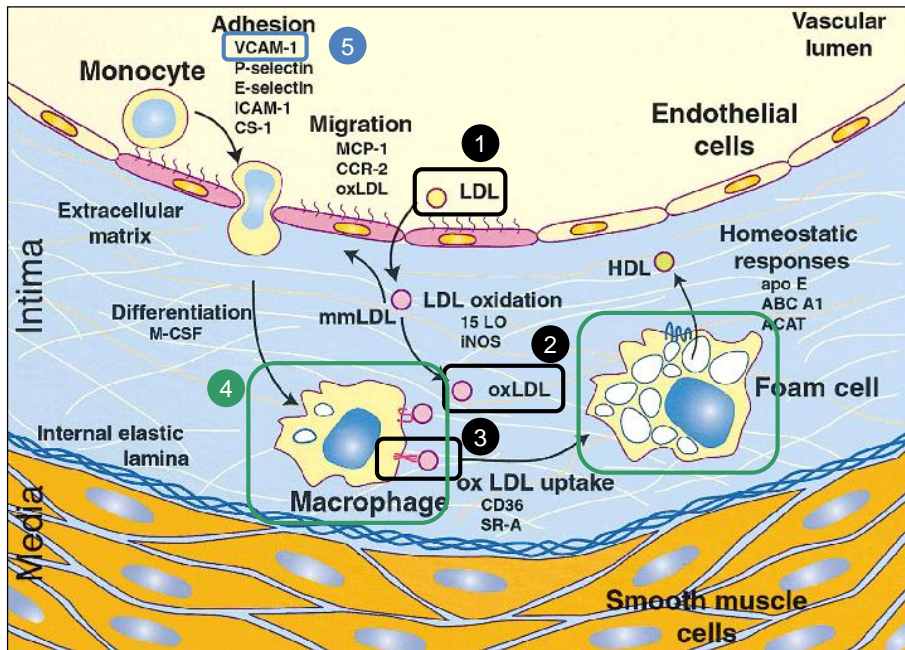
Target	Tracer	Nature of tracer
1. LDL	[ <sup>123</sup> I] [ <sup>99m</sup> Tc] [ <sup>111</sup> In]-LDL	Lipoprotein
2. OxLDL	[ <sup>99m</sup> Tc]-oxLDL [ <sup>123</sup> I]-SP4 [ <sup>99m</sup> Tc]-P199 [ <sup>125</sup> I]-MDA2 [ <sup>125</sup> I]-IK17 [ <sup>124</sup> I]-CD68Fc	Lipoprotein Oligopeptide Oligopeptide Antibody Antibody Peptide
3. LOX-1	[ <sup>99m</sup> Tc]-LOX1-mAb [ <sup>99m</sup> Tc]- mAb/Lipo [ <sup>99m</sup> Tc]-LOXsdAb	Antibody Antibody & liposome nanobody
4. Macrophages	[ <sup>18</sup> F]-FDG [ <sup>18</sup> F] [ <sup>11</sup> C]-Choline [ <sup>11</sup> C]-PK11195 [ <sup>99m</sup> Tc]-EC20 [ <sup>18</sup> F]-FDM [ <sup>111</sup> In]-monocytes [ <sup>99m</sup> Tc]-mononuclear [ <sup>64</sup> Cu]-TNP [ <sup>99m</sup> Tc]-MCP-1 [ <sup>68</sup> Ga]-DOTATATE	Carbohydrate Amino alcohol organic peptide carbohydrate Cells Cells Nanoparticle Peptide Organic
5. VCAM-1	[ <sup>99m</sup> Tc]-B2702p [ <sup>18</sup> F]-4V [ <sup>99m</sup> Tc] [ <sup>18</sup> F]-cAbVCAM1-5	Peptide Peptide nanobody
6. MMPs	[ <sup>123</sup> I]-HO-CGS27023A [ <sup>99m</sup> Tc]-mAb MT1	Hydroxamate der. Antibody
7. Apoptosis	[ <sup>99m</sup> Tc]-Annexin A5 [ <sup>99m</sup> Tc]-Ap <sub>4</sub> A	Protein Purine analog
8. Angiogenesis	[ <sup>111</sup> In]-RP748 [ <sup>18</sup> F]-galacto-RGD [ <sup>125</sup> I]-L19 [ <sup>125</sup> I]-G11	peptidomimetic peptidomimetic Antibody Antibody
9. Oncogene act	[ <sup>99m</sup> Tc]-ASONS	Antisense nucleotide
10. Thrombosis	[ <sup>99m</sup> Tc]-mAb T. Factor [ <sup>99m</sup> Tc]-fucoidan [ <sup>111</sup> In]-Platelets	Antibody Polysaccharide Platelets
11. Lymphocytes	[ <sup>99m</sup> Tc]-IL2	Interleukin
12. Calcifications	[ <sup>18</sup> F]-NaF	Inorganic
13. CD40 Ligand	[ <sup>125</sup> I]-StrepNP31	Peptide

# Evalués chez l'homme



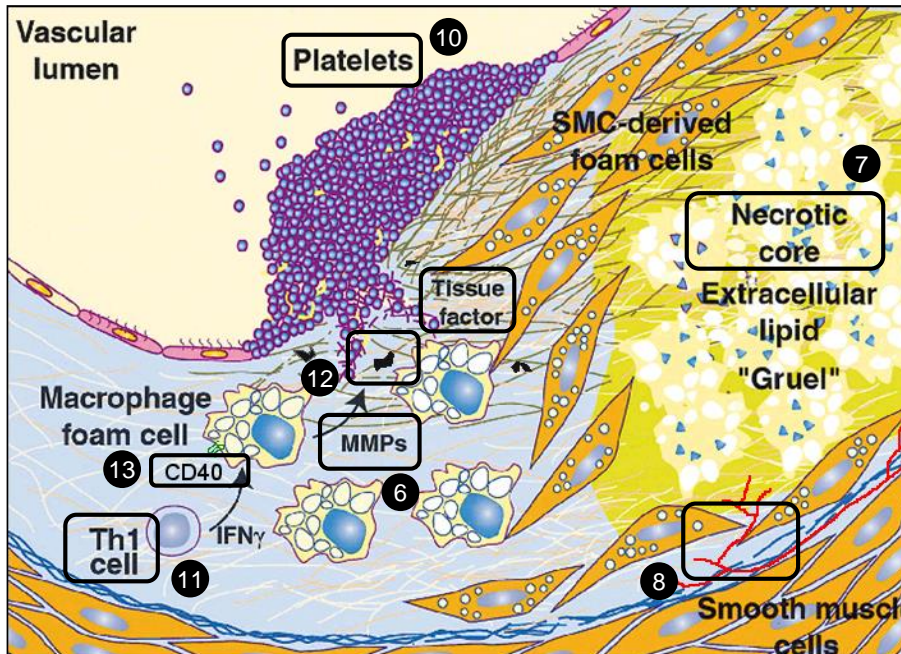
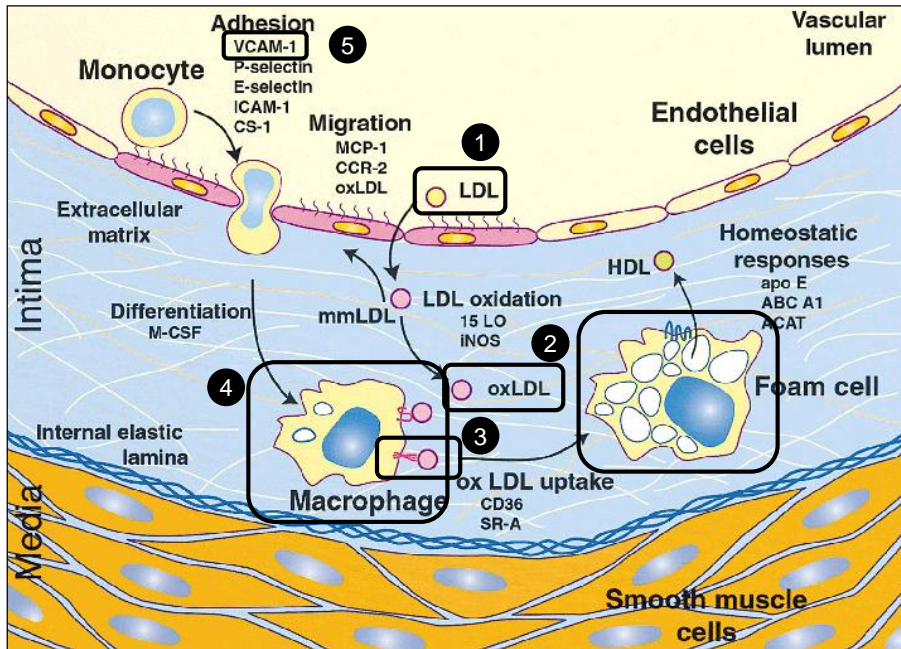
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# Evalués chez l'homme/ Transfert clinique



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# Routine clinique

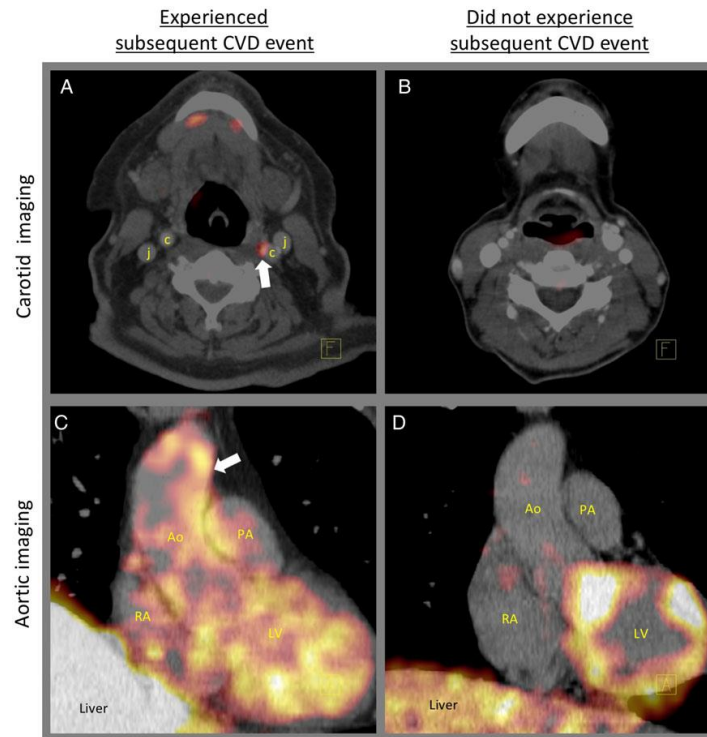


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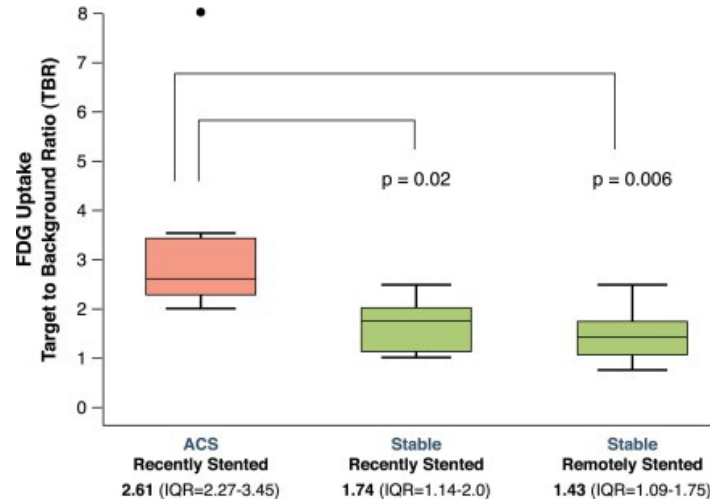
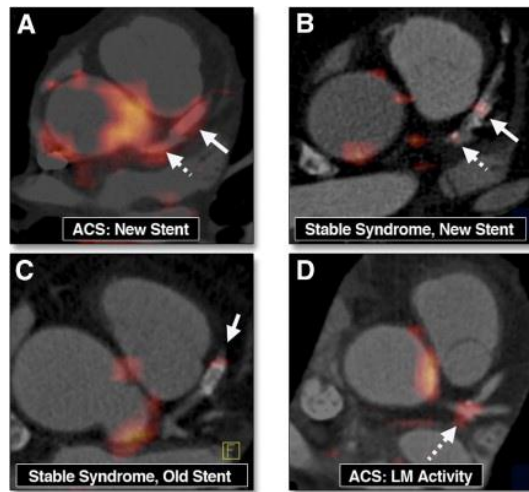
# $^{18}\text{F}$ FDG : imagerie des macrophages

- Capté par les macrophages (M1>M2)
- Captation carotidienne corrélée avec les régions riches en macrophages.
- Permet d'imagerie des plaques dans les artères périphériques.



Joseph and Tawakol. *European Heart Journal* 2016

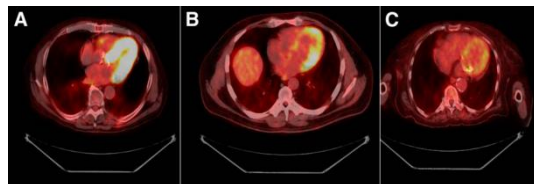
# $^{18}\text{F}$ FDG : imagerie coronaire?



Rogers et al. JACC cardiovascular imaging. Vol3 n4 2010.

25 patients (10 ACS, 15 stables)

⇒ L'imagerie des artères coronaires est possible

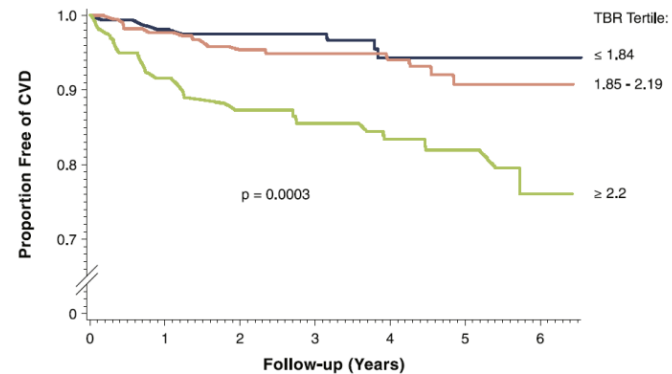
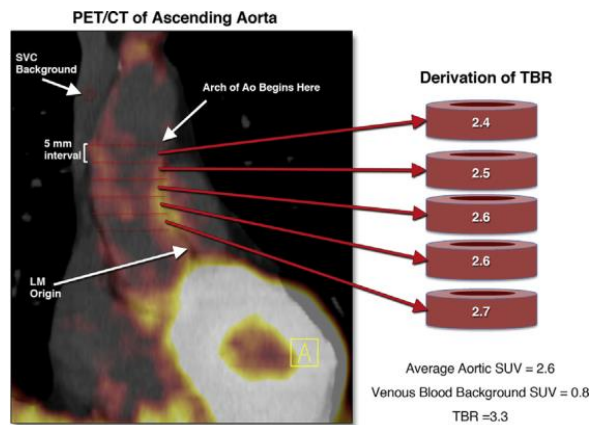


🔒 jeûne et/ou régime hyperlipidémique carencé en carbohydrates ⇒ 32 patients: 37% bon, 25% adéquate, 37% mauvais.

Wykrzykowska et al. J Nucl Med 2009; 50:563-568

# $^{18}\text{F}$ FDG : artères périphériques

Mesure au niveau de l'aorte ascendante: étude retrospective



	Number at Risk:						Adjusted HR:	
TBR Tertile 1:	167	160	149	120	75	36	10	1.0 (Referent)
TBR Tertile 2:	224	216	199	170	112	58	14	1.36 (0.55, 3.35)
TBR Tertile 3:	122	108	101	92	74	40	14	4.71 (1.98, 11.2)

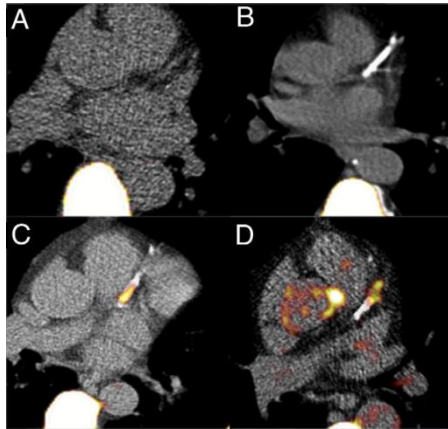
513 patients

Suivie moyen: 4,2 ans

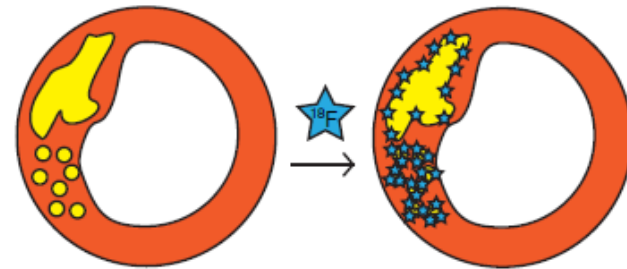
44 CVD

⇒ Améliore la prédiction de la survenue de CVD indépendamment du score de Framingham.

# $^{18}\text{F}$ -Fluorure de sodium (NaF)



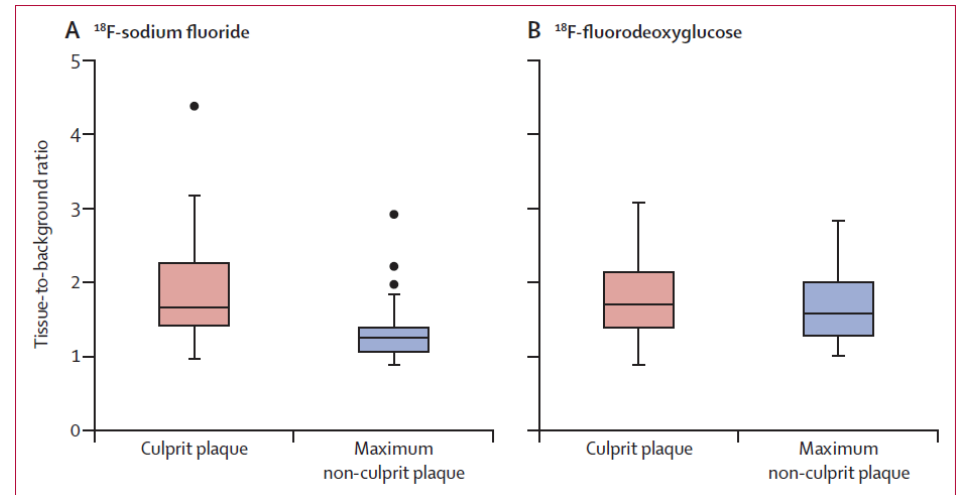
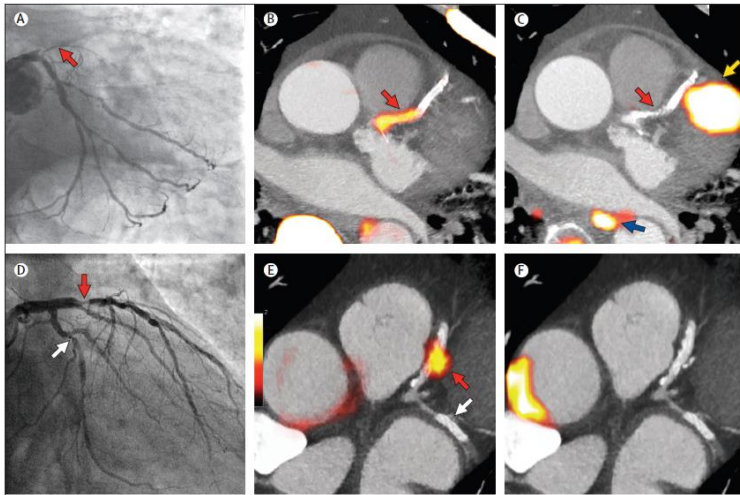
*Dweck et al. JACC 2012; 59: 1539–48*  
119 patients



*Irkle. Nat Commun. 2015 Jul 7;6:7495*

- ⇒ L'imagerie des coronaires est possible
- ⇒ Corrélié au score calcique ( $r=0,652$   $P<0,001$ ) MAIS:
  - 40% des macrocalcification visibles au CT uniquement
  - microcalcifications ( $<50\mu\text{m}$ ) visibles au NaF uniquement
- ⇒ Corrélation avec des antécédents de CVD ( $p=0,016$ ) et Framingham ( $p=0,011$ )

# $^{18}\text{F}$ -Fluorure de sodium (NaF)



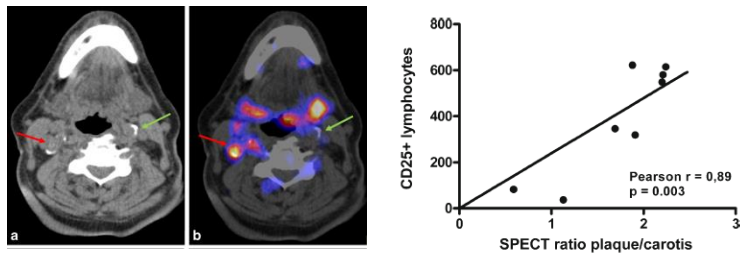
Joshi et al. *Lancet* 2014; 383: 705–13

80 patients (40 infarctus du myocarde, 40 angors stables)

- ⇒ Identification des plaques rompues et à haut risque.
- ⇒ Plus performant que le  $^{18}\text{F}$ FDG

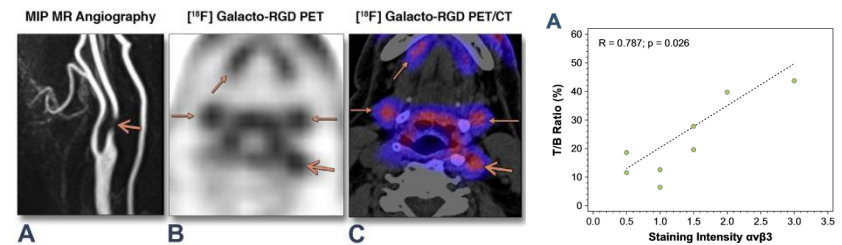
# Autres radiotraceurs évalués chez l'homme

## $^{99m}\text{Tc}$ -II2 : Lymphocytes



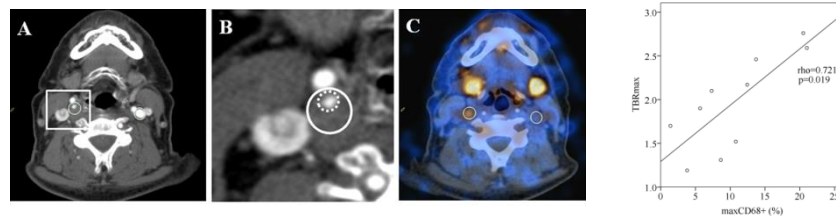
*Eur J Nucl Med Mol Imaging (2014) 41:1710–1719*

## $^{18}\text{F}$ -Galacto RGD : $\alpha_v\beta_3$



*JACC : Cardiovascular Imaging (2014) :178 – 87*

## $^{18}\text{F}$ -choline : macrophages



*Circ. Cardiovascular imaging 2016 May;9(5)*

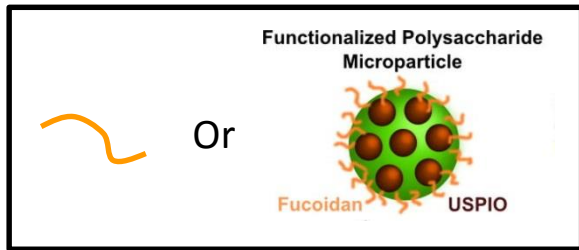
10 patients avec endarterectomie:

Le signal corrèle avec le niveau d'expression de la cible

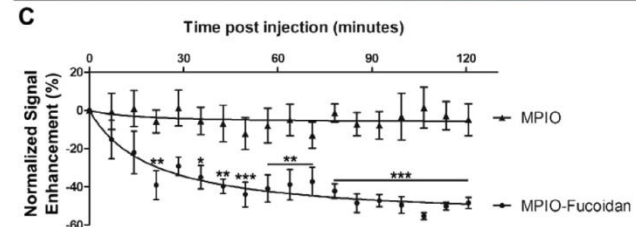
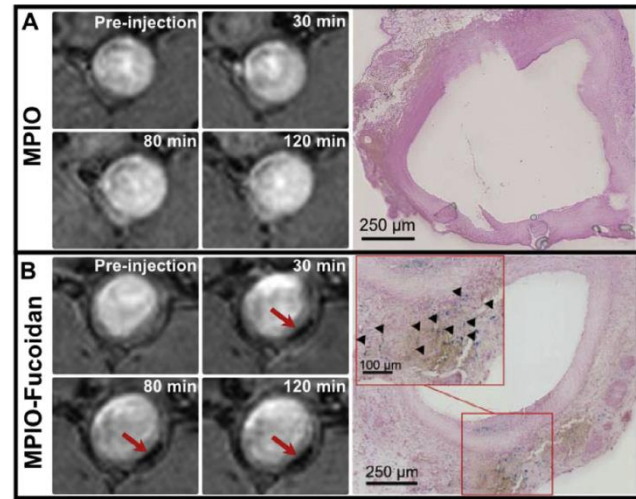
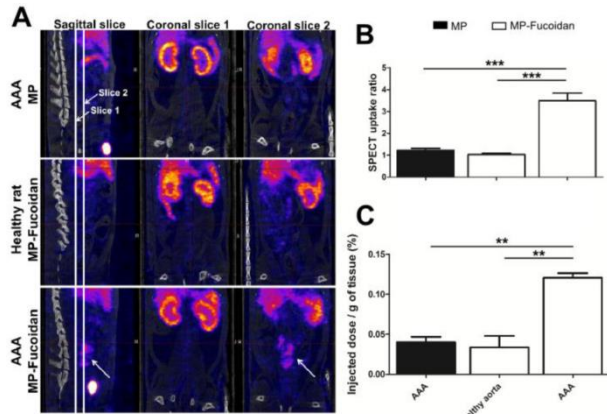
⇒ études prospectives à suivre

# $^{99m}\text{Tc}$ -Fucoïdan

Low Molecular Weight Fucoïdan (LMWF): imagerie de la P-selectin (thrombus)

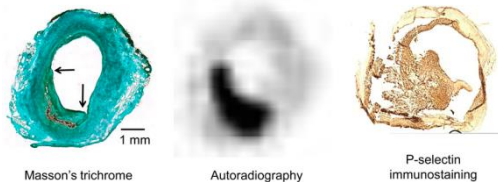


Nucléaire



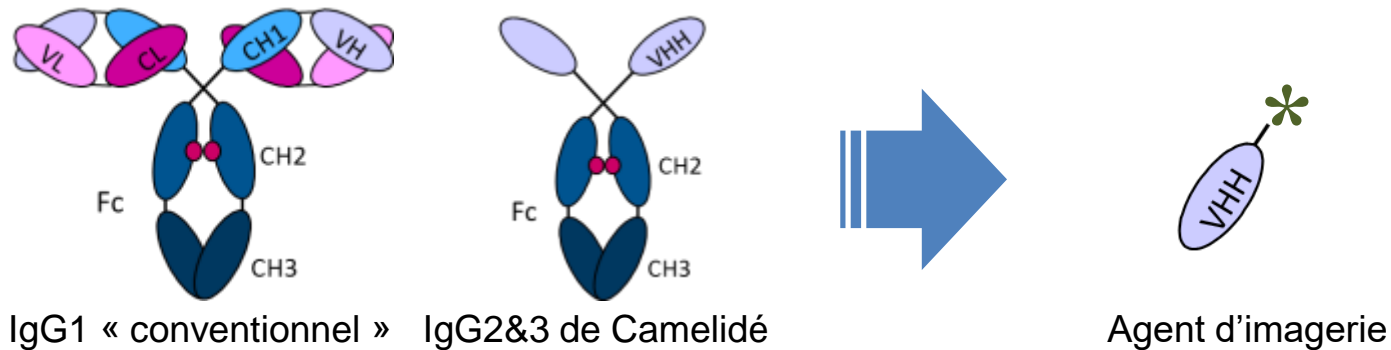
*Acta Biomaterialia* 10 (2014) 3535–3545

Theranostics 2014, Vol. 4, Issue 6



➤ Transfert clinique. **FucoThrombo** (RPIB 2013)

# Single-Domain Antibodies (nanobodies, VHH)



## LETTERS TO NATURE

### Naturally occurring antibodies devoid of light chains

C. Hamers-Casterman, T. Atarhouch, S. Muyldermans, G. Robinson\*, C. Hamers, E. Bajyana Songa, N. Bendahman & R. Hamers†

Vrije Universiteit Brussel, Instituut voor Moleculaire Biologie, Paardenstraat 65, B-1640 Sint Genesius Rode, Belgium

\* Department of Biochemistry, Trinity College, Dublin 2, Ireland

Nature. 1993 363(6428):446-8

## \* Nucléaire

- SPECT:  $^{99m}\text{Tc}$ ,  $^{111}\text{In}$ ,  $^{125/123}\text{I}$
- PET:  $^{68}\text{Ga}$ ,  $^{18}\text{F}$ ,  $^{64}\text{Cu}$
- Therapie:  $^{177}\text{Lu}$

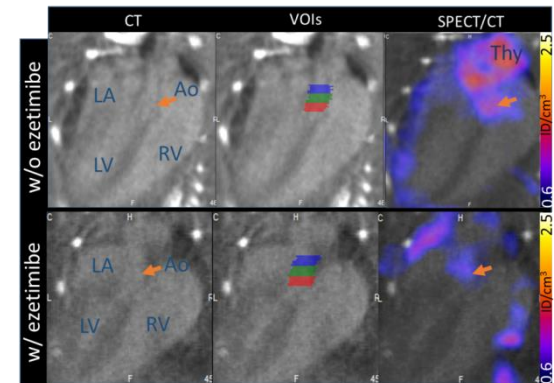
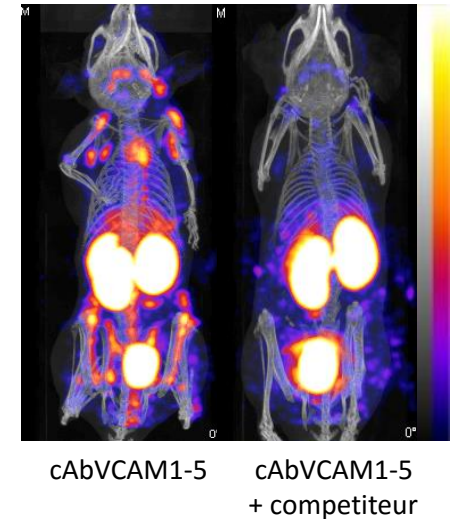
## \* Optique

## \* Ultrasons

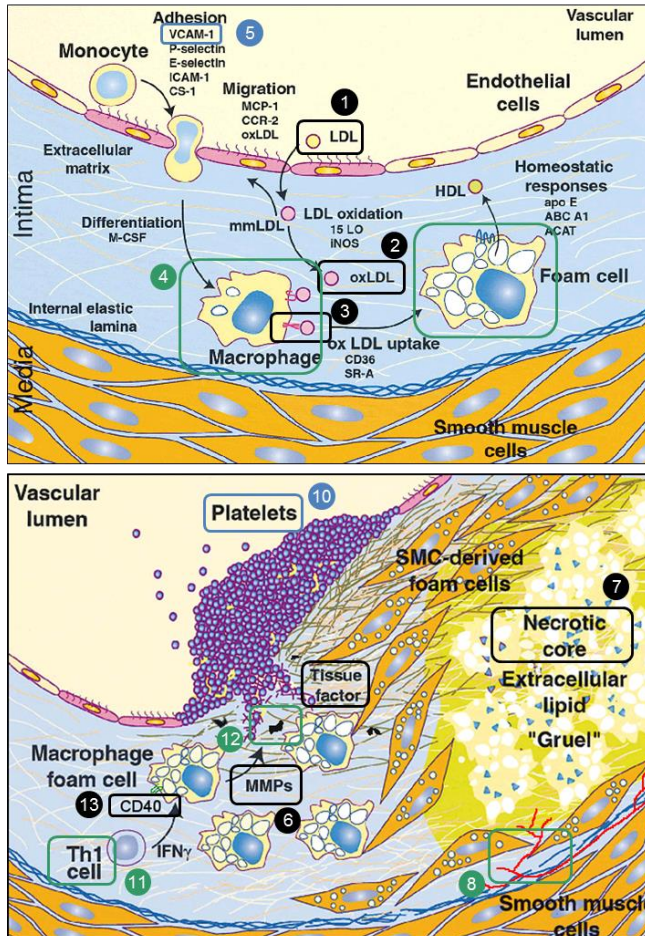


# $^{99m}\text{Tc}$ -cAbVCAM1-5

- 1<sup>ère</sup> application pour l'imagerie cardiovasculaire
- Validation de cAbVCAM1-5
  - ✓ **Cross réactivité:** VCAM-1 murin/humain(nM)
  - ✓ **Élimination sanguine rapide**
  - ✓ **Stabilité:** *in vitro* & *in vivo*
  - ✓ **Spécificité:** *in vitro* & *in vivo*
  - ✓ **Sensibilité:** *Statine* & *Ezetimibe*
- **Transfert clinique (PRTS 2013)**  
injection à l'homme Q1 2017



# Conclusion



Target	Tracer	Nature of tracer	
1. LDL	[ <sup>123</sup> I] [ <sup>99m</sup> Tc] [ <sup>111</sup> In]-LDL	Lipoprotein	
2. OxLDL	[ <sup>99m</sup> Tc]-oxLDL	Lipoprotein	
	[ <sup>123</sup> I]-SP4	Oligopeptide	
	[ <sup>99m</sup> Tc]-P199	Oligopeptide	
	[ <sup>125</sup> I]-MDA2	Antibody	
	[ <sup>125</sup> I]-IK17	Antibody	
3. LOX-1	[ <sup>124</sup> I]-CD68Fc	Peptide	
	[ <sup>99m</sup> Tc]-LOX1-mAb	Antibody	
	[ <sup>99m</sup> Tc]- mAb/Lipo	Antibody & liposome	
	[ <sup>99m</sup> Tc]-LOXsdAb	nanobody	
4. Macrophages	[ <sup>18</sup> F]-FDG	Carbohydrate	
	[ <sup>18</sup> F] [ <sup>11</sup> C]-Choline	Amino alcohol	
	[ <sup>11</sup> C]-PK11195	organic	
	[ <sup>99m</sup> Tc]-EC20	peptide	
	[ <sup>18</sup> F]-FDM	carbohydrate	
	[ <sup>111</sup> In]-monocytes	Cells	
	[ <sup>99m</sup> Tc]-mononuclear	Cells	
	[ <sup>64</sup> Cu]-TNP	Nanoparticle	
	[ <sup>99m</sup> Tc]-MCP-1	Peptide	
	[ <sup>68</sup> Ga]-DOTATATE	Organic	
	5. VCAM-1	[ <sup>99m</sup> Tc]-B2702p	Peptide
		[ <sup>18</sup> F]-4V	Peptide
	6. MMPs	[ <sup>99m</sup> Tc] [ <sup>18</sup> F]-cAbVCAM1-5	nanobody
[ <sup>123</sup> I]-HO-CGS27023A		Hydroxamate der.	
7. Apoptosis	[ <sup>99m</sup> Tc]-mAb MT1	Antibody	
	[ <sup>99m</sup> Tc]-Annexin A5	Protein	
8. Angiogenesis	[ <sup>99m</sup> Tc]-Ap <sub>5</sub> A	Purine analog	
	[ <sup>111</sup> In]-RP748	peptidomimetic	
9. Oncogene act	[ <sup>18</sup> F]-galacto-RGD	peptidomimetic	
	[ <sup>125</sup> I]-L19	Antibody	
	[ <sup>125</sup> I]-G11	Antibody	
10. Thrombosis	[ <sup>99m</sup> Tc]-ASONS	Antisense nucleotide	
11. Lymphocytes	[ <sup>99m</sup> Tc]-mAb T. Factor	Antibody	
	[ <sup>99m</sup> Tc]-fucoidan	Polysaccharide	
12. Calcifications	[ <sup>111</sup> In]-Platelets	Platelets	
	[ <sup>99m</sup> Tc]-IL2	Interleukin	
13. CD40 Ligand	[ <sup>18</sup> F]-NaF	Inorganic	
	[ <sup>125</sup> I]-StrepNP31	Peptide	

⇒ Un challenge important

⇒ Des traceurs en évaluation clinique ou en cours de transfert clinique



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