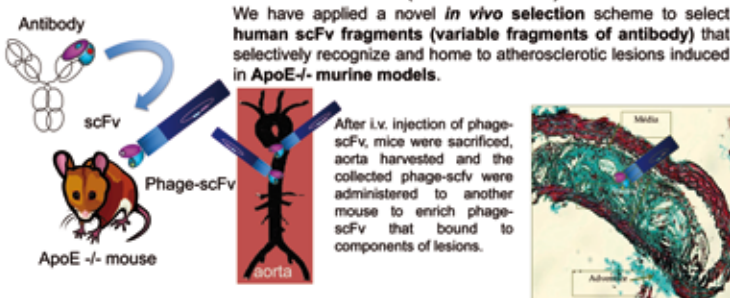


## Development of smart bioagents armed for molecular imaging of vulnerable plaques in atherosclerosis

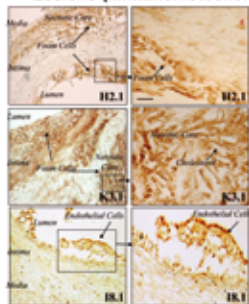
### Context/Objectives

IMATHABIO project aimed at developing a diagnostic approach for atherosclerosis which is the main cause of death in the Western world and tends to increase rapidly in developing countries. Atherosclerosis is a chronic, progressive inflammatory disease, which is initiated in response to invading pathogenic lipoprotein in the arterial wall. Atherosclerotic arteries have morphologically raised lesions, referred to as **atherosclerotic plaques**. The lesions evolve to vulnerable plaques presenting large lipid cores covered by a thin fibrous cap at high risk of rupture and thrombi formation, thus precipitating the clinical conditions of stroke and myocardial infarction. Nowadays, there is an increasing interest to diagnose atherosclerosis before this advanced stage. **Human antibodies coupled to contrast agents for MRI (Magnetic Resonance Imaging) or to radiotracers for SPECT (Single Photon Emission Computed Tomography)** meet the need for an accurate and innocuous targeting of the cellular components that underlie the risk of rupture.

### In vivo phage display to select human antibodies in atherosclerotic models (UMR 5536)



### Soluble human scFv Homing to Atherosclerotic Lesions (Immunohistochemistry)

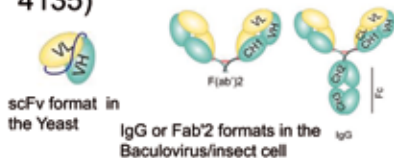


### Proteomic for identification of the targets (immunoprecipitation of the antigen and mass spectroscopy)

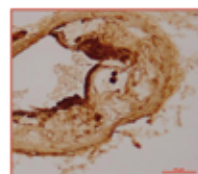
Human scFv	K3-1	H2-1
Target	Carbonic anhydrase 2	Serpin B3? S100-A9?

Such tissue-specific homing ligands have led to the characterization of **new up-regulated lesion-associated markers**. These novel experiments represent an entirely new approach to **identification of lesions-specific ligands and the cognate targets**.

### Human antibody engineering (UPS 3044; EA 4135)

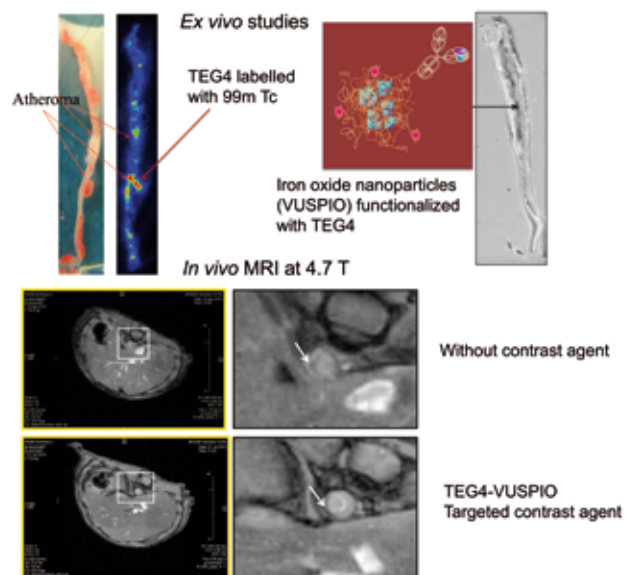


These systems have been successfully implemented in IMATHABIO for a **large scale production of anti-platelets human antibodies**. A high production rate is a mandatory condition for further imaging studies.



TEG4, a human IgG anti-platelets antibody that targets atherosclerotic lesions

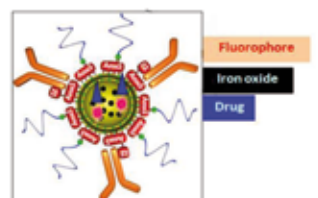
### Imaging: SPECT and MRI (UPR 9048; UMR5536; IBA (CisBio international))



Axial T2-weighted images of an atherosclerotic ApoE-/- mouse, TEG4-VUSPIO is detected by a loss of MRI signal generated by iron oxide accumulation in the atherosclerotic vessel wall.

### Conclusions-perspectives-impact

This approach opens the way to **Theranostic strategies** based on **non-invasive molecular imaging and selective drug delivery** for early detection of atherogenesis. IMATHABIO impacts on the submission of **ATHERANHUMAB** project to ANR RPIB with new collaborations including the firms Millegen and Atoxigen respectively skilled in human antibody selection and toxicity studies and a new academic partner (UMR 5248, CBMN) skilled in nanovector design.



Nanovectors (Magneto-liposomes functionalized with Anx5-ZZ-IgG) armed for therapy

### Publications-Valorisation

MRI of inducible P-selectin expression in human activated platelets involved in the early stages of atherosclerosis. Jacobin-Valat MJ, Deranchia K, Monnet S, Hagemeyer CE, Bonetto S, Robert R, Biran M, Massot P, Miraux S, Sanchez S, Boucier-Sore AK, Franconi JM, Duguet E, Clofent-Sanchez G. *NMR Biomed* Dec 2010.

Rapid screening of purification strategies for the capture of a human recombinant F(ab')2 expressed in baculovirus-infected cells using a micro-plate approach and SELDI-MS. Pezzini J, Brenac Brochier V, Barnouillet MP, Cerruti M, Clofent-Sanchez G, Schapman A, Topoli A, Robert R, Cabanne C, Cerruti P, Santarelli X. *J Chromatogr B Analyt Technol Biomed Life Sci* 2009;877(24):2428-2434.

Identification of new human antibody fragments homing to atherosclerotic endothelial and subendothelial tissues by *in vivo* phage display. Kamel Deranchia, Marie-Josée Jacobin-Valat, Amélie Vallet, Hervé Bazin, Xavier Santarelli, Stéphane Sanchez, Pierre Dos Santos, Jean-Michel Franconi, Stéphane Bonetto and Gisèle Clofent-Sanchez. *Presentation selected in Bième congrès de la NFSA (Avignon) : 16-19 Juin 2011*

Paper submitted in *Am J Pathol*

Nanoparticles functionalised with the recombinant human antibody TEG4 for *in vivo* detection of atherosclerotic plaque by Magnetic Resonance Imaging. Marie-Josée Jacobin-Valat, Jeanny Laroche-Traineau, Martine Cérutti, Stéphane Monnet, Marc Biran, Stéphane Sanchez, Jean-Michel Franconi, Gisèle Clofent-Sanchez.

Oral communications : RITS GRAMM 2011(6-8 Avril 2011 ; Rennes) ; Bième congrès de la NFSA (16-19 Juin 2011 ; Avignon)

Homings to Atherosclerotic Lesion : Access to New Pairs of Antibodies/Targets by *in Vivo* Phage Display Biopanning. K Deranchia, A Vallet, M-J Jacobin-Valat, S Sanchez, J-M Franconi, G Clofent-Sanchez, S Bonetto

20th Annual International Conference on Antibody Engineering - San Diego, CA-December 6-10, 2009

Magnetic Resonance Imaging of inducible P-Selectin expression in human platelets involved in thrombi formation. Jacobin-Valat MJ, Deranchia K, Monnet S, Hagemeyer CE, Bonetto S, Robert R, Biran M, Massot P, Miraux S, Sanchez S, Boucier-Sore AK, Franconi JM, Duguet E, Clofent-Sanchez European Society of Magnetic Resonance in Medicine and Biology (ESMRMB). Oral communication orale, Valence (Espagne) ; 1-5 oct 2008

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