

mMRI[®] (molecular MRI) for the Detection of Vulnerable Plaques

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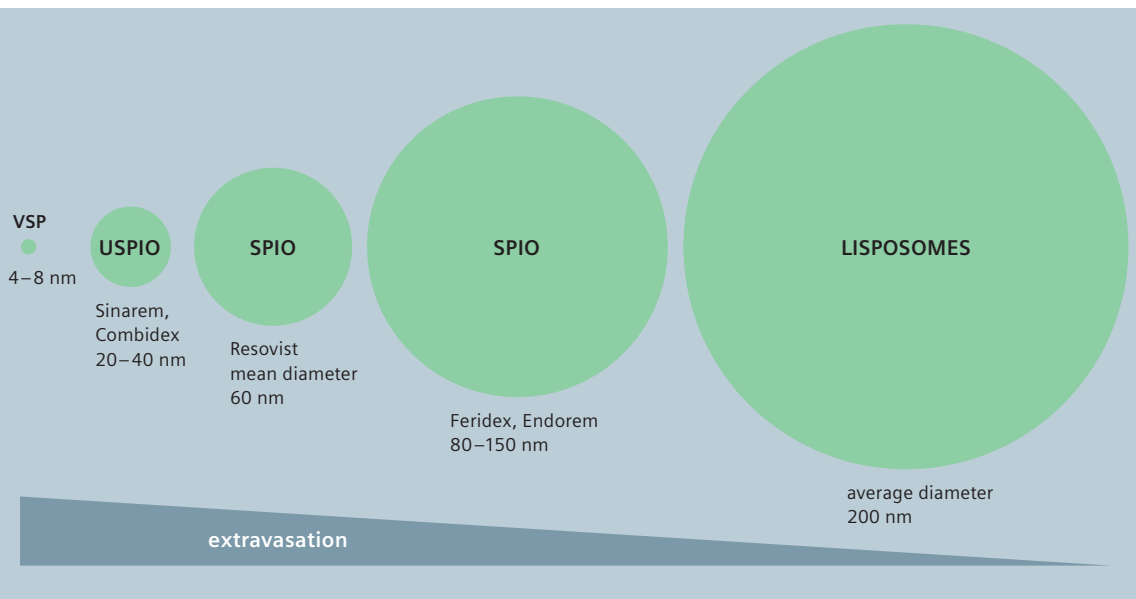
There is evidence that sudden coronary events or stroke are caused by vulnerable atherosclerotic plaques. Vulnerable plaques are atherosclerotic lesions due to endothelial inflammations, that may rupture and induce thrombus formation. Subsequent myocardial ischemia and acute myocardial infarction is considered to be responsible for approximately 60–70% of cardiac deaths. Determining the degree of stenosis by angiogram, currently the routine method relied on for clinical decision making, is unreliable for risk stratification. Thus a differentiation of stable or unstable atherosclerotic plaque burden is currently not possible with non-invasive imaging methods, although techniques like contrast enhanced CT can visualize plaque composition to some degree.

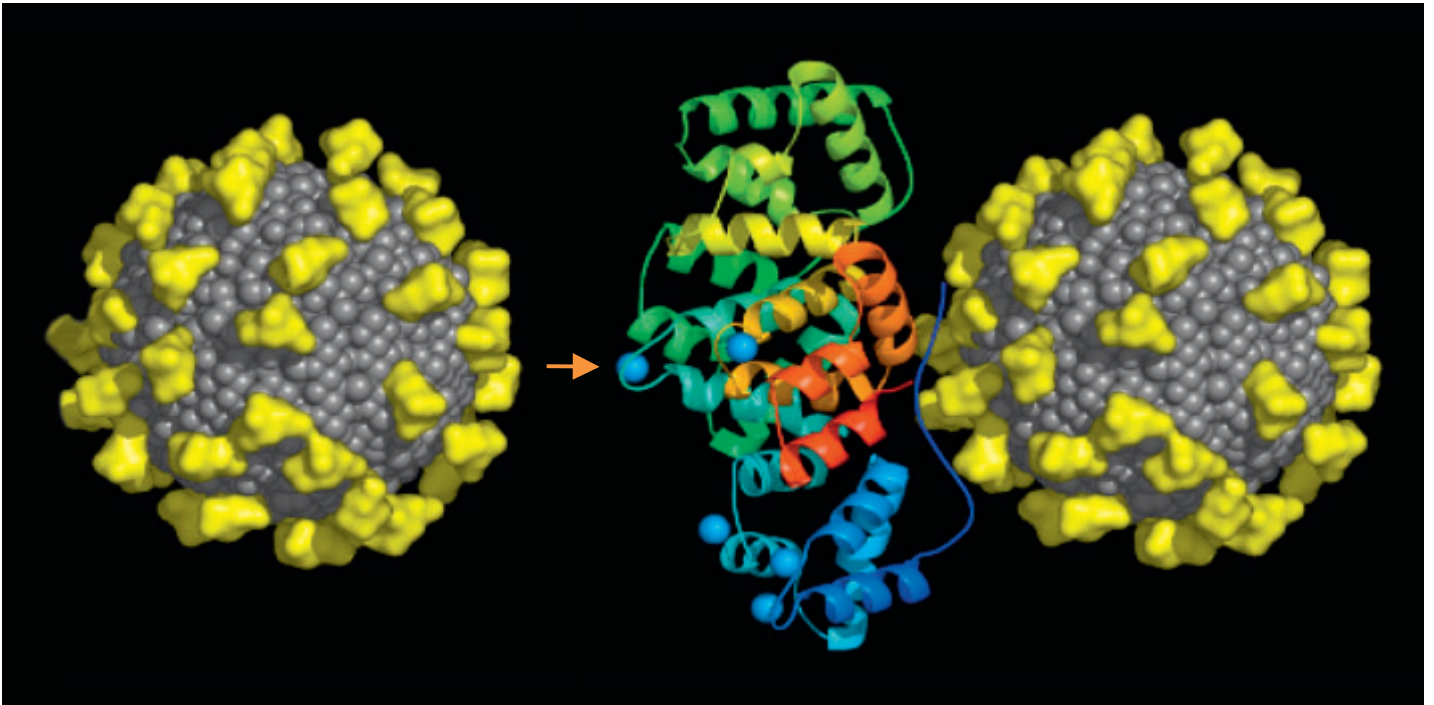
Major pathomorphologic characteristics of plaque vulnerability are the thickness of the fibrous cap, increased vessel wall angiogenesis, migration of inflammatory cells like macrophages, and degra-

ation of connective tissue along with a decrease in smooth muscle cells. Several molecular biomarkers are associated with vulnerable plaque formation such as adhesion molecules, matrix metalloproteases, cathepsins and integrins.

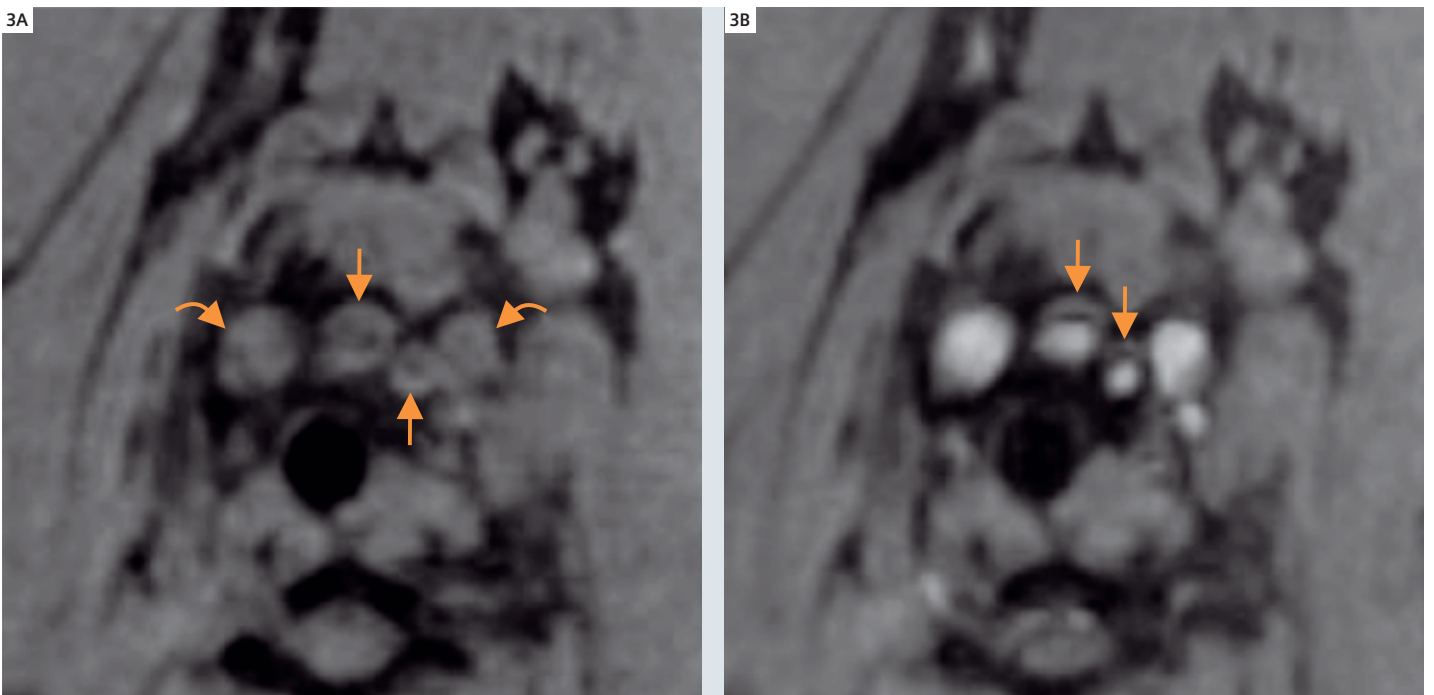
The aim of the „Nano_AG“ project is to develop a new class of targeted, electrostatically stabilized iron oxide contrast agents. The development is based on Very Small Iron Oxide Particles (VSOP) developed by Ferropharm GmbH, Berlin, Germany. In contrast to well-known polymer-based iron oxide nano-particles like USPIO or SPIO the size of the newly developed electrostatically stabilized iron oxide nanoparticles has been further decreased to a size less than 4 nm in diameter. This allows for extravasation and renal elimination (~30%). In addition, the bio-availability for targeting various pathologic tissues is highly optimized, while the high magnetic properties for MRI are retained. Pre-clinical proof-of-principle studies demonstrated

1 Size comparison of different particles as markers for molecular imaging.

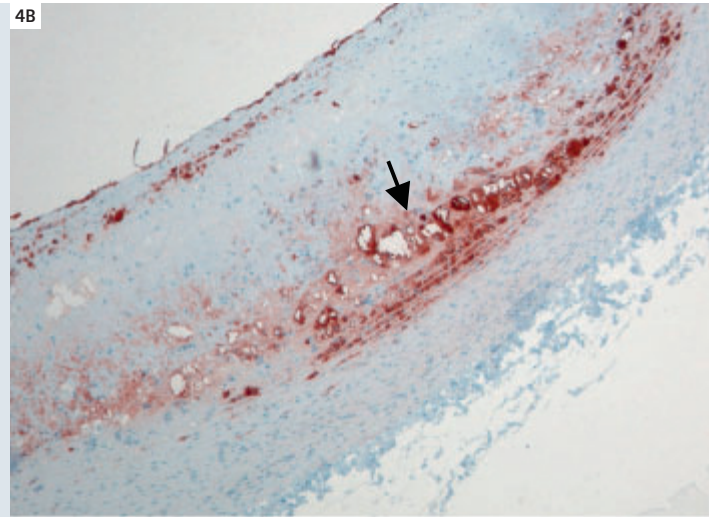
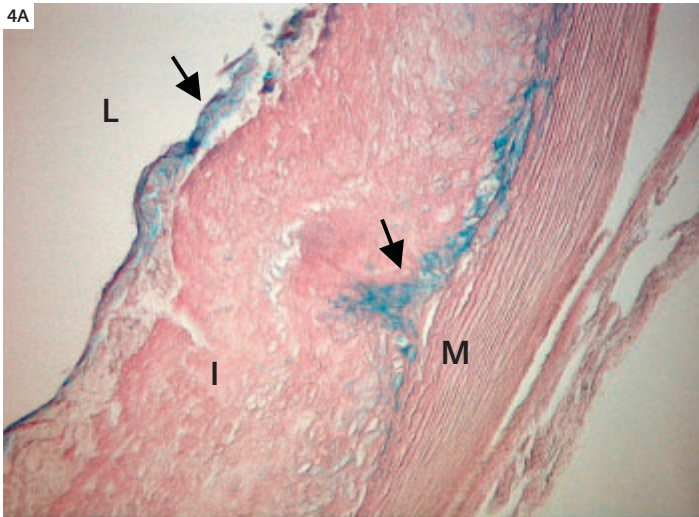




2 VSOP particle with yellow molecules indicating the citrate bound to the iron oxide surface (grey). Functionalization of the particle by specific peptides e.g. Annexin V. (Kindly provided by Eyk Schellenberger, Radiology, Charité, Berlin.)



3 MRI in axial section orientation of the brachio-cephalic trunk and the left common carotid artery (arrows) of a rabbit before (A) and after (B) administration of VSOP at a dose of 0.06 mMol Fe/kg. Images have been obtained at a Siemens MAGNETOM 1.5 T scanner with a commercially available 4-channel body array coil using a flow-saturated ECG-gated segmented 3D GRE sequence. Luminal signal increase demonstrates free circulation particles which exhibit a strong T1-relaxation time shortening effect. Arterial vessel wall of the left common carotid artery and the right brachiocephalic trunc (arrows in fig. 3B) exhibit a strong signal loss in contrary to the vessel wall of the veins (curve arrows in fig. 3A).



4 (A) Prussian-blue staining of a section from the brachiocephalic trunk 2 hours after administration of VSOP at a dose of 0.06 mmol Fe/kg bw. Areas positive for prussian blue staining are demonstrated in the subendothelial layer and in the area of the intimomedial interface (L = lumen, I = intima, m = media).

(B) Presence of cells positive for RAM-11 antibody with tissue integrity loss in the intimomedial interface could as well be seen in these regions reflecting the complex and advanced pathologic character of this arterial athero-sclerotic lesion. According to the data published by Moreno et al. the intimomedial interface damage could be attributed to rupture-prone vulnerable lesions (Moreno et al. 2002 *Circulation* 105, 21: 2504–2511).

that these VSOP are a valuable tool for the characterisation of atherosclerotic plaque burden and the evaluation of high-risk atherosclerosis by magnetic resonance imaging (MRI).

Nano_AG seeks to optimize VSOPs for vulnerable plaque imaging further by targeting of vulnerable plaque biomarkers. This shall be achieved by linking peptides to VSOPs.

A major aspect of the work of Nano_AG is to obtain mMRI® (molecular MRI) contrast agents which facilitate a fast translation into clinical trials. Development from bench to bedside within a reasonable timeframe is possible only by using biocompatible components which already have been approved. This has been taken into account and the targeted VSOPs are composites of well characterized building blocks: iron oxide, citrate and biologically occurring peptides.

Nano_AG develops further sensitive measurement protocols with high spatial and temporal resolution. This includes off-resonance imaging and navigator sequences, which are mandatory to detection small contrast agent concentrations within the coronaries. Dedicated small animal imaging adaptations for clinical MRI devices have been applied to facilitating preclinical studies in a clinical setting to speed up translational research.

The Nano_AG consortia consists of Siemens Medical Solutions (project manager), the Charité in Berlin, the German Cancer Research Center (DKFZ) in Heidelberg, Freiburg University, MeVis in Bremen, Ferropharm and Bayer Schering Pharma, both in Berlin. Nano_AG is partly funded by the BMBF (German Ministry of Education and Research) grant „Nano for Life“.

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