Nanomedicine, the research field that makes use of nanoparticulate agents for biomedical applications, is well established in oncology. In fact, the application of nanotechnology in medicine started with, and is most prominently present in, targeted therapeutics for cancer. The initial goals included altering pharmacokinetics, increasing the percentage of injected dose to reach the tumor, accomplishing target-specific delivery and uptake therefore decreasing doses of compounds with antitumor activity. Furthermore, nanoparticles may be used to solubilize hydrophobic or amphiphilic molecules. Many nanoparticulate formulations (eg, cytostatic agents) have been shown to exhibit increased therapeutic efficacy and diminished adverse effects, which have ultimately resulted in their clinical application. The most well-known nanoparticulate formulations applied are liposomes (bilayered vesicles of phospholipids) which can contain a hydrophilic payload in their lumen or an amphiphilic payload in the lipid bilayer. Doxil, a liposomal formulation of doxorubicin, is approved for the treatment of solid tumors in patients with breast-carcinoma metastases, and has resulted in a subsequent improvement in survival. Gene targeting to angiogenic tumor blood vessels using cationic liposomes specific for \( \alpha \beta 3 \)-integrin has shown efficacy in tumor bearing mice. Using this approach, apoptosis of the tumor-associated endothelium was induced by a mutant \( \text{Raf} \) gene, ultimately leading to tumor cell apoptosis and sustained regression of established primary and metastatic tumors. More recently, a synergistic approach that focuses on cutting of the blood supply of the tumor and killing tumor cells was realized using so-called nanocells, nanoparticles that contain both an angiostatic and a cytostatic drug.

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In the late 1990’s, advances in molecular biology and genetics in general and the establishment of the “molecular imaging” research field in particular led to a resurgent interest in nanoparticle targeting. To this aim, nanoparticles, specifically targeted to epitopes of interest, were loaded with contrast generating material to allow their detection by diagnostic imaging. The early reports primarily focused on cancer, but in the beginning of the 21st century, the first reports about the use of nanoparticles for molecular imaging of cardiovascular disease appeared.

For example, molecular MRI of macrophages in atherosclerosis has been accomplished using ultrasmall particles of iron oxide or paramagnetic immunomicelles. More recently, Hyafil et al have shown the possibility to image macrophages in atherosclerotic plaques with computed tomoscopy imaging using N1177, a nanoparticulate formulation of iodine. Molecular imaging of other important features of atherosclerosis, ie, thrombus, plaque angiogenesis, and lipoproteins has also been accomplished using paramagnetic nanoparticles.

Several multimodality molecular imaging studies of cardiovascular disease related processes, including apoptosis after myocardial infarction and the overexpression of cell adhesion molecules in atherosclerosis, have been realized using superparamagnetic cross-linked iron oxide nanoparticles that were additionally labeled for fluorescence or nuclear imaging. These studies revealed the significance of integrating multiple properties within one nanoparticle to allow exploitation of the strengths of the different imaging modalities used. These differences may be related to sensitivity, spatial and temporal resolution, or the ability to image multiple targets simultaneously.

All the aforementioned developments have revolutionized the application of nanotechnology in cardiovascular pathologies and have led to improved understanding of the possibilities for drug delivery to diseased tissue, eg, atherosclerotic plaques. In 2006 Winter et al from the Washington University School of Medicine (St Louis) reported plaque angiogenesis inhibition using paramagnetic perfluorocarbon nanoparticles that were loaded with fumagillin, while molecular imaging was used as a noninvasive read-out for therapeutic efficacy. This type of nanoparticle, schematically depicted in the Figure, is able to characterize and interfere in the dynamics of cardiovascular disease in a number of ways. The targeting ability and nature of its payload allows it to both “capture” and act on the specified tissue while allowing its activity to be “captured” by noninvasive imaging modalities such as MRI.

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, a report from the same St Louis investigators demonstrates another innovative application of \( \alpha \beta 3 \)-specific paramagnetic nanoparticles. After angioplasty, vascular stenosis may reoccur. This restenosis process may be inhibited by placing drug eluting stents (DES) that locally release antiproliferative agents. However, there are some serious limitations to DES, such as their placement and inhibited endothelial healing. Cyrus et al developed an innovative approach to locally deliver rapamycin via \( \alpha \beta 3 \)-specific nanoparticles without the use of a stent. As a model, they used hyperlipidemic rabbits that underwent injury of the...
femoral artery using an angioplasty cathether. The injured arteries were incubated locally for a short period of time with the nanoparticles by temporally blocking the blood flow using vascular snares. After thorough washing to remove unbound nanoparticles, the blood flow was reestablished. MRI was used to determine stenosis and, because of the paramagnetic properties included in the formulation, was also used to visualize nanoparticle delivery. Two weeks after treatment, MRI revealed the occurrence of restenosis in the femoral arteries treated with control agents, whereas the αβ3-specific nanoparticle treated femoral arteries displayed no lumen irregularities. These in vivo findings were validated histologically and revealed significantly less atherosclerotic plaque formation in the treated arteries as compared to controls. Importantly, and in contradiction with what is normally observed after placing DES, endothelial healing occurred within 4 weeks.

The study by Cyrus et al demonstrates another useful and innovative application of nanotechnology in cardiovascular disease. Although the incubation approach using vascular snares poses a limitation on the applicability, systemic exposure of rapamycin is minimized, likely diminishing serious adverse effects related to this drug. In previous studies it was demonstrated that αβ3-specific perfluorocarbon nanoparticles also specifically target plaques after intravenous administration which would allow the delivery of rapamycin to vessel areas that cannot be locally incuoted.

The general concept of using nanoparticulate agents in cardiovascular disease has gained increasingly wider acceptance because of advances in target-specific molecular imaging. Combinatory therapy and imaging approaches are extremely useful in assessing agent delivery as well as therapeutic efficacy. Therefore, it may be anticipated that nanomedicine and noninvasive imaging will continue to contribute to improved diagnosis and treatment of atherosclerosis and cardiovascular disease in general.23

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**References**


Nanomedicine Captures Cardiovascular Disease
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