CARDIOVASCULAR NANOMEDICINE: *A POSSE AD ESSE*

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The main idea behind the current thematic issue of the *Methodist DeBakey Cardiovascular Journal* on cardiovascular nanomedicine is to emphasize the growing relevance of the field and the potential of nanotechnology to revolutionize current clinical practice. In this editorial, we will provide a brief history of the field of biomedical nanotechnology and introduce some of the topics that will be highlighted in this issue.

Nanotechnology can be defined as the science of synthetic/engineerable objects with unique characteristics that emerge due to the objects' nanoscopic dimensions or imperative functional components.[1] Another fundamental element in this definition is the ability to sustain and explain the observed unique behavior on the nanoscale by a mechanism of action. Currently, nanotechnology is a fast-rising area of research gaining support from scientists in the academic, industry, and regulatory/federal sectors. In fact, since its establishment in 2001, the cumulative National Nanotechnology Initiative (NNI) program investment (including the 2012 request) now totals approximately $16.5 billion, reflecting the program's broad support from the U.S. Congress (see *www.nano.gov* for more information).

The field of nanotechnology was foreseen by Nobel Laureate Richard Feynman in 1959. In his legendary and visionary speech, "There's plenty of room in the bottom," Dr. Feynman shared his dream of manipulating objects on a submicron scale. Forty years later, Richard Smalley — who received a Nobel Prize in 1996 for the discovery of the fullerene carbon-60 molecule — stated that "human health has always been determined on the nanometer scale; this is where the structure and properties of the machines of life work in every one of the cells in every living thing."[2]

Nanomedicine synergistically cross-fertilizes the concepts of nanofabrication, chemistry, biology, and medicine, synthesizing new and emergent technologies with the ultimate goal of gaining precise control over the biological processes occurring on a submicron scale. In the past few decades, nanomedicine has progressively developed into a strong multidisciplinary field,[3] enabling prominent technological advances such as intelligent materials and substances with durable surface coating, faster electronics, responsive biosensors, targeted therapeutic nanovectors, and improved nanodiagnostics. Unmet needs in medicine provide an opportunity to develop new, nanoscience-enabled, sophisticated technologies. A critical challenge facing contemporary medicine is the personalization of therapy. Personalized medicine can be defined as an individualized treatment strategy developed for a specific patient based on results from that patient's clinical samples, including sophisticated diagnostic imaging and genomic and proteomic analysis. Due to its ability to direct processes on the subcellular level, nanomedicine is considered one of the main potential enablers of personalized patient care.[4, 5]

Despite significant progress in managing cardiovascular disorders (CVD), molecular mechanisms underlying pathological conditions such as plaque formation remain largely unclear. As a result, early detection is difficult, leading to a high rate of morbidity and mortality. Advanced applications of nanotechnology for ex vivo diagnostic and in vivo imaging tools and marker/contrast-agents are being refined with the goal of detecting disease at its early stages.[6] Ultimately, imaging at the level of a single cell, combined with the ability to monitor the effectiveness of therapy, will provide accurate diagnosis not only at an earlier disease stage but ideally before the onset of symptoms. In fact, the development of nanomaterials that have the ability to interact with matter at the submicron scale could potentially extend subcellular and molecular detection beyond the limits of conventional diagnostic techniques

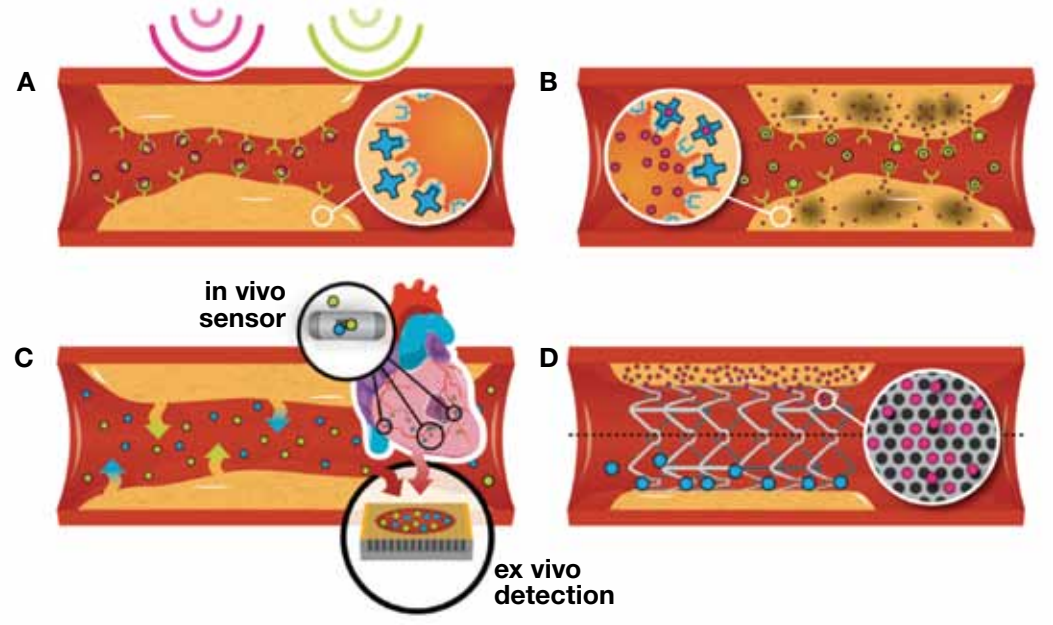

Figure 1. Schematic presentation of various nanotechnological approaches for advanced CVD diagnosis and therapy: Nanoparticles for (A) multimodal image contrast and (B) improved treatment of CVD can be targeted to immune cells or the specific ligands presented on the inflamed endothelium of the atherosclerotic plaque; (C) in vivo sensors implanted in the pericardial region or on one of the main blood vessels and techniques for ex vivo biomarker detection; (D) nanostructured drug-/nanoparticle-eluting stents.

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(Figure 1C). This would provide personalized information that could be used to assess risk for developing a pathological condition, further aiding in the optimization of individualized therapy. These types of point-of-care (POC) devices, such as bio-nanochips, will be reviewed in depth later in this issue.

Another application of nanotechnology to CVD involves nanotextured materials. Nanotextured stent coatings, e.g., titania[7] and hydroxyapatite,[8] have been applied to enhance endothelial cell attachment and proliferation for the reendothelialization of vascular walls. Moreover, due to their nanoporous morphology, these stents can be used for loading and controlled release of therapeutic substances (Figure 1D).

While the therapeutic potential of many novel agents on the molecular scale is indisputable, several roadblocks can hamper their clinical performance. These include unfavorable physico-chemical properties (e.g., water insolubility) and a multiplicity of biological barriers that prevent therapeutic and diagnostic contrast agents from reaching their destinations. As a result, the diseased tissue accumulation of molecularly targeted agents following intravenous administration is extremely low (0.01% to 0.001% of the injected dose).[9] This means that higher doses of the agents must be administered to patients for sufficient therapeutic response, creating a narrow efficiency/toxicity therapeutic window.[10] Thus, the perfect agent should be equipped with a number of imperative characteristics, including stability in biological milieu, proper solubility, and preferential accumulation at the disease loci, to list a few.[11, 12] Obviously, no single molecule can simultaneously deal with these tasks.

These considerations fueled the development of nanovectors, which are designed to overcome the intrinsic biophysical barriers and improve clinical outcomes. A nanovector is a nanoscale particle or integrated system that delivers therapeutics or contrast agents. Currently, nanovectors are being developed and investigated as carriers for personalized therapeutic and imaging contrast agents based on the simultaneous, anticipated advantages of homing at the diseased site (such as atherosclerotic plaque, cancer lesions, etc.), schematically presented in Figures 1A and 1B. This behavior relies on the nanovector's ability to cross the various obstacles, or biobarriers, located between the administration site and the target organ. Historically, nanotechnology has made the most prominent contributions to the field of oncology. During the last 15 years, nanocarriers occupied an important niche in the treatment of cancer patients, with liposomes being the first commercially available drug nanocarrier for injectable therapeutics.[3, 13, 14] Liposomal doxorubicin was granted FDA approval in the mid-1990s for use against Kaposi's sarcoma. Henceforth, a range of therapeutic nanovectors with a variety of compositions and physico-chemical properties, including geometry and surface functionalizations, went through different stages of development.[15, 16] This investment of effort generated a gigantic "nano toolbox" that encompasses various vectors and countless combinations of the above, thus clear considerations should be taken when developing a carrier for a specific drug or condition. The rational design of nanovectors for CVD[12, 17] will be further discussed in this issue, as will the development of magnetically driven nanoparticles[18] and nanoparticles for blood pool imaging.[19]

Other applications of nanotechnology in the field of CVD include the use of novel nanomaterials for enhanced tissue regeneration and in vivo monitoring of the conditions. For example, precise control over the mechanisms for stem cell recruitment and activation can drastically enhance regeneration of injured vessels and heart muscle in the case of atherosclerosis or myocardial infarction. It is envisioned that novel therapies will include intelligent nanobiomaterials with the ability to attract cultured or intrinsic stem cells to the site of injury. Currently, scaffold-guided tissue regeneration can be achieved by nanopatterning the implant surfaces.

In 2003, The National Heart, Lung, and Blood Institute (NHLBI) convened a working group of researchers to review the challenges and opportunities offered by nanotechnology for CVD (*www.nhlbi.nih.gov/meetings/nano_sum.htm*). Chaired by Dr. Ferrari, the working group encompassed physicians, engineers, chemists, and biologists who shared the vision of applying nanoscience to overcome challenges associated with therapy and diagnosis of heart, lung, and blood-related disorders. Nanotherapeutics, molecular imaging, POC diagnostics and biosensors, and tissue engineering and biomaterials were considered by the working group to be fields where nanotechnology was expected to have a very pronounced impact. The group's findings were reported in the seminal paper in the field of cardiovascular nanomedicine entitled "Recommendations of the National Heart, Lung, and Blood Institute Nanotechnology Working Group."[20] The primary recommendation of the group was to facilitate interdisciplinary research between the nanotechnology and nanoscience communities and researchers working on CVD and lung disorders. Therefore, in 2005, the NHLBI opened a Program of Excellence in Nanotechnology (PEN) with a specific goal to bring together scientists from complementary disciplines to enable the translation of cutting-edge discoveries in nanoscience and nanotechnology research to the diagnosis, treatment, and management of an array of related diseases. Based on the progress made since the original funding in 2005, the NHLBI in 2010 awarded $65 million to renew its Programs for Nanotechnology Research. The four current PEN awards involve teams spread across 17 institutions (*www.nhlbi-pen.net/centers/gatech.html*) and are focused on translation of technological advances achieved in the previous years into clinical practice. For example, one of the PENs involves researchers from Washington University in St. Louis, Texas A&M University, University of California–Berkley, University of California–Santa Barbara, and Southwestern Medical Center in Dallas. This center aims to produce nanomaterials tailored with specific sizes, shapes, and compositions to provide for enhanced imaging and treatment of acute lung injury and atherosclerosis.[21-23] Other centers with home institutions in Massachusetts General Hospital, Georgia Institute of Technology, and Mount Sinai Medical School/ Massachusetts Institute of Technology are developing nanoscience-based tools to (1) image and deliver therapeutics and regeneration factors to atherosclerotic plaque[24] and damaged heart tissue, respectively; (2) enhance stem cell-mediated repair of damaged heart tissue[25]; and (3) create a POC system for the rapid detection of pulmonary infections and CVD.[26]

With continued innovations in imaging, biomaterials, tissue-targeted nanovectors, biosensors, and personalized therapies, nanomedicine can offer cardiologists and surgeons new avenues to improve patient care and to diagnose and treat CVD with higher efficiency.[27] These potential advantages are summarized in Figure 2.

Overall, the manuscripts in this issue of the *Methodist DeBakey Cardiovascular Journal* will introduce readers to various subcategories of cardiovascular nanomedicine research that present mechanisms and potential clinical impact. We hope that this special issue will foster collaborations and fuel further research in this relatively new but very promising area of science.

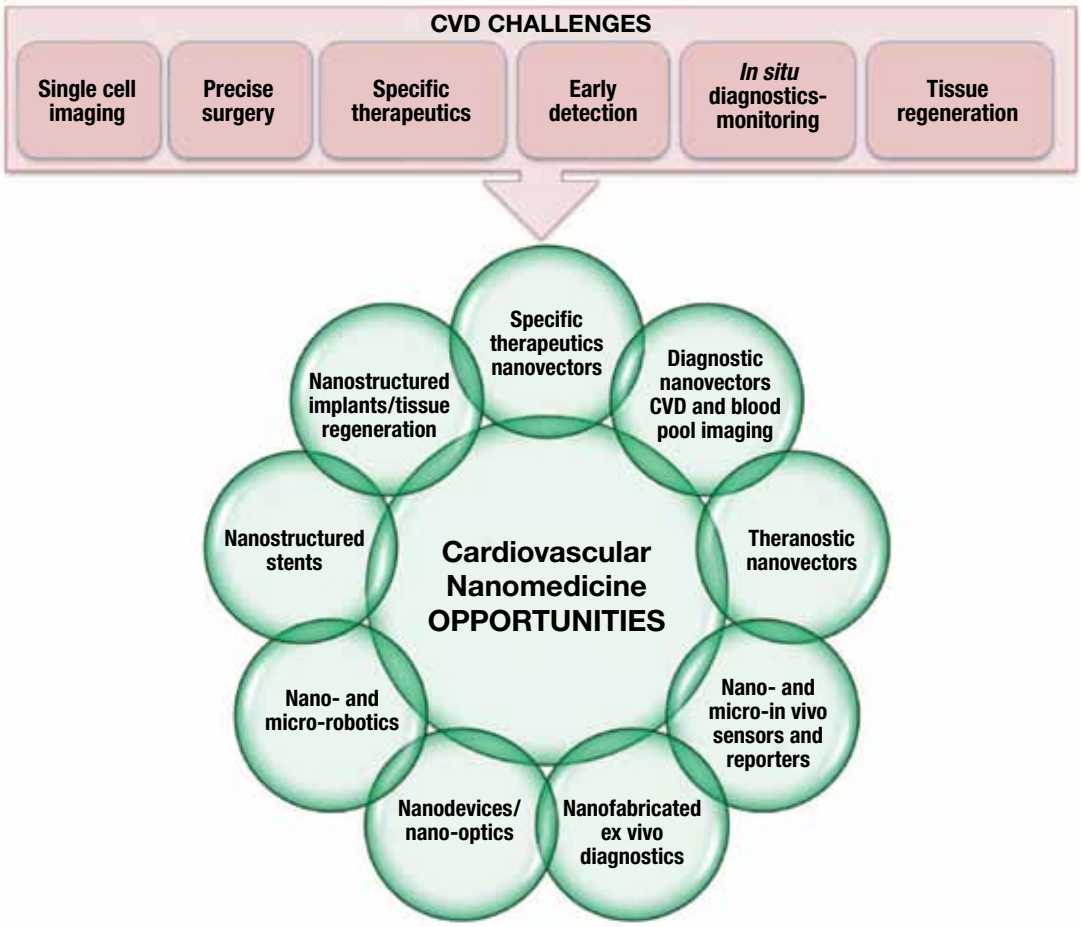

Figure 2. Summary of challenges in diagnosis and therapy of CVD and opportunities of nanomedicine to intervene.

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