# NANOTHERAPEUTIC SOLUTIONS FOR CARDIOVASCULAR DISEASE

John P. Cooke, M.D., Ph.D.; Johnique Atkins, Ph.D.
*Houston Methodist Research Institute, Houston, Texas*

What is a "nanotherapeutic solution?" In this special issue of the *Methodist DeBakey Cardiovascular Journal,* we have arrived at a unique interface between the fields of cardiovascular science and nanotechnology, where exciting and unexpected insights are occurring. Nanotechnology is the field that deals with objects at the nanoscale level (1 to 100 nm). To put this into perspective, the DNA helix is about 2 nm in width. By contrast, human cells are measured in microns (i.e., thousands of nanometers). Thus, hundreds to thousands of nanoparticles would fit comfortably into a red blood cell (one such nanoparticle in red blood cells is the hemoglobin molecule, which is about 5 nm in diameter). Synthesizing, characterizing, manipulating, and imaging these nanoparticles requires cutting-edge technologies. Atomic force microscopy and scanning tunneling microscopy permit the visualization of nanoparticles, and innovations such as nanoimprint lithography and atomic layer epitaxy permit synthesis of nanostructures.

The application of nanotechnology to human health has been termed "nanomedicine." With respect to heart and vascular diseases, nanotechnology has the potential for widespread use: Research may be directed toward diagnosis (as with implantable nanoelectronic biosensors), drug therapy (as with nanoparticles that deliver cardiovascular drugs), or nanodevices (as with nanopatterned vascular stents). For example, delivery of cardiovascular therapeutics with nanoparticles might enhance the localization of the drugs in the affected tissue. The nanoparticles—which are composed of silica, lipids, carbon nanotubes, dendrimers, proteins, and/or nucleic acids—could be generated with features that may selectively bind to diseased tissues and/or protect the drug from metabolism, thereby reducing both the drug dosage and systemic exposure while attaining a therapeutic effect.

## Who Are the Pioneers in Nanotherapeutic Solutions?

The pioneers of nanotherapeutic solutions are not individuals but highly integrated multidisciplinary teams that include materials scientists, bioengineers, electrical and mechanical engineers, biochemists, physicists, tissue engineers, molecular biologists, and physician-scientists in translational and clinical research. For this issue of the *Methodist DeBakey Cardiovascular Journal,* we have assembled such a team from Northeastern University and the Houston Methodist Research Institute. What draws this group together are a common mission of developing nanotherapeutic solutions for cardiovascular disease and a single man who has done much for this field. As part of his dedication to translational research excellence, George Kostas and his family have made generous gifts to Houston Methodist Research Institute (HMRI) and Northeastern University toward nanotechnology and nanomedicine. At Northeastern University, the George J. Kostas Nanoscale Technology and Manufacturing Research Center was established in 2005. This 7,000-square-foot facility includes cleanrooms and instruments for nanofabrication processes and characterization and has been a catalyst for collaboration and invention. At HMRI, the George and Angelina Kostas Research Center for Cardiovascular Nanomedicine supports collaborative research between cardiovascular scientists and nanoengineers with seed grants and symposia to foster synergistic investigation. In addition, the gift supports research collaborations between the two institutions in the area of cardiovascular nanomedicine, in part through an international meeting held each year.

## The Rationale for Cardiovascular-Based Nanotherapeutic Solutions

In the past half century, much progress has been made in understanding the pathobiology of cardiovascular diseases, and many new and effective therapies have reduced the morbidity and mortality of heart and vessel disorders. Despite this, cardiovascular disease remains the major cause of mortality in the Western world, and there remains a need for more efficacious therapies. With this in mind, our goal is to highlight emerging nanotherapeutics that have the potential to revolutionize the treatment of cardiovascular diseases by providing therapies that target different pathologies (e.g., inflammation) and drug delivery systems with the ability to overcome the biological challenges of current therapies. To this end, we have assembled leaders and collaborators in the area of nanotherapeutics and cardiovascular sciences to share their insights and research.

In this issue of the *Methodist DeBakey Cardiovascular Journal*, Deshpande and colleagues lead off by exploring the promise of nucleic acid-based therapies to reestablish a functional endothelium. With the ability to reprogram or restore gene function, nucleic acid-based therapies appear to be well suited for targeting endothelial dysfunction in cardiovascular disease. Stability issues and poor permeability across cellular membranes limit the adequate delivery of nucleic acids to disease sites, thus limiting their therapeutic success. Nanoparticle solutions to deliver DNA, RNA, and oligonucleotides are being developed to overcome these challenges and are discussed in this review.

This is followed by the article "Local Inhibition of Macrophage and Smooth Muscle Cell Proliferation to Suppress Plaque Progression" by Sukhovershin and coworkers, who describe the pathobiology of atherosclerosis and how this knowledge may be leveraged to design nanotherapeutic solutions. Macrophages and smooth muscle cells (SMCs) proliferate and are major contributors to the growth of atherosclerotic plaque, making them natural targets for novel therapies. Using nanotechnology to specifically target macrophage- and SMC-mediated inflammation without causing systemic toxicity is a promising strategy to suppress plaque progression.

Pownall and colleagues have spent a lifetime researching the biochemical characterization of lipoproteins and how they may be used as nanoparticles for therapeutic application. In "Native and Reconstituted Lipoproteins in Nanomedicine: Physicochemical Determinants of Nanoparticle Structure, Stability, and Metabolism," Pownall and colleagues discuss the use of lipidic particles, including liposomes, lipoproteins, and reconstituted high-density


**The Kostas family:** The Kostas's generous gifts allowed Houston Methodist Research Institute and Northeastern University to establish state-of-the-art nanomedicine and nanotechnology research centers. From left to right: Georgina Kostas Nichols, George Kostas, Pam Kostas Walker, and Cynthia Kostas.

lipoproteins (rHDL) as potential carriers of water-soluble, hydrophobic, and amphiphilic molecules. These nanoparticle-based drug delivery systems can overcome the challenges of appropriate drug targeting and maintaining drugs at therapeutic levels that arise with many therapeutic molecules. The authors also summarize the properties of human plasma lipoproteins and rHDL, explain the physicochemical determinants of lipid transfer between biological surfaces and membranes, and discuss strategies for increasing the amount of time these molecules can survive in the plasma.

In the area of endothelial integrity and cardiovascular disease, Wong et al. review the influence of shear stress on endothelial function and its influence on the development and progression of atherosclerosis. Laminar flow has beneficial effects on endothelial biology, mediated in part by shear stress-inducible microRNAs. Early data suggests that these microRNAs suppress processes involved in atherosclerosis. Wong and his group have recently developed an E-selectin-targeted platform that enriches therapeutic microRNAs in the inflamed endothelium to inhibit formation of vascular lesions in preclinical models.

Also in this issue is an interesting review by Yilmaz and colleagues titled "Novel Nanoprinting for Oral Delivery of Poorly Soluble Drugs." Up to 70% of newly developed drugs are poorly water soluble, which may reduce absorption when taken orally. To overcome this challenge, researchers must employ new and effective delivery systems since the oral route is preferred for patient compliance and cost considerations. Incorporating poorly water soluble drugs into nano-sized drug carriers is one such strategy. The authors describe a recently developed nanomanufacturing process called "nanoprinting" that is expected to be more effective and less toxic than current strategies. If successful, this technique can be used to deliver promising drug candidates that have poor water solubility, including many cardiovascular drugs.

Drug-eluting stents are an effective therapy for arterial obstructions and have reduced the incidence of restenosis over first-generation bare metal stents. However, they also inhibit the growth of endothelial cells needed to cover the stent and reduce inflammatory responses. In the article titled "Enhancing Stent Effectiveness with Nanofeatures," Bassous and colleagues discuss current developments in nanomaterials that have the potential to overcome the challenges of current stents by reducing restenosis, enhancing reendothelialization, and improving drug delivery.

The issue ends with a review by Molinaro et al. titled "Vascular Inflammation: A Novel Access Route for Nanomedicine," which discusses the role of endothelial inflammation in the pathogenesis of cardiovascular disease. Chronic systemic inflammatory conditions such as obesity, autoimmune diseases, cancer, and infectious diseases play an important role in cardiovascular disease by inducing endothelial inflammation and thus creating niches for disease initiation and progression. Current therapies may have cardiovascular benefit in part because of their associated anti-inflammatory effects. Inflamed endothelium represents a viable target due to the altered phenotype of adhesive surface markers and increased endothelial permeability. Accordingly, the article highlights novel nanotherapeutic approaches that can exploit inflamed endothelium by passively or actively targeting diseased tissue to enhance cardiovascular treatment.

This special issue documents some of the progress being made at the interface of nanotechnology and cardiovascular sciences. Our hope is to illuminate the many emerging novel nanotherapeutic solutions being developed to reduce morbidity and mortality and ultimately transform the treatment of cardiovascular diseases.