Chapter 10
Nanocardiology

Introduction

Nanocardiology is the application of nanobiotechnology to cardiovascular diseases. Recent rapid advances in nanobiotechnology offer a wealth of new opportunities for diagnosis and therapy of cardiovascular diseases (Jain 2011a). As far back as 2003, the National Heart, Lung, and Blood Institute, USA, convened a working group on nanotechnology for translational applications to heart, lung, blood disorders, and cardiovascular complications of sleep apnea to solve clinical problems.

Nanotechnology-Based Cardiovascular Diagnosis

Nanobiotechnology has refined molecular diagnosis, and this applies to detection of cardiovascular diseases also. Availability of genotyping and detection of single nucleotide polymorphisms (SNPs) will provide information on risks of developing genetically linked cardiovascular diseases. Application of nanodiagnostics in pharmacogenetics will be used for selection and guidance of appropriate therapy for an individual patient. This will facilitate the development of personalized medicine.

Biomarkers play an important role in diagnosis of cardiovascular disorders, particularly myocardial infarction (Jain 2010). Detection of biomarkers, particularly using proteomic technologies, has also been refined by nanobiotechnology.

Detection of Biomarkers of Myocardial Infarction in Saliva by a Nanobiochip

The feasibility and utility of saliva as an alternative diagnostic fluid for identifying biomarkers of acute myocardial infarction (AMI) has been investigated. A lab-on-a-chip method was used to assay 21 proteins in serum and unstimulated

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whole saliva procured from AMI patients within 48 h of chest pain onset and from apparently healthy controls (Floriano et al. 2009). Both established and novel cardiac biomarkers demonstrated significant differences in concentrations between patients with AMI and controls. The saliva-based biomarker panel of C-reactive protein (CRP), myoglobin, and myeloperoxidase showed diagnostic capability, which was better than that of ECG alone. When used in conjunction with ECG, screening capacity for AMI was enhanced and was comparable to that of a panel of brain natriuretic peptide, troponin I, creatine kinase-MB, and myoglobin. To translate these findings into clinical practice, the whole saliva tests were adapted to a nanobiochip platform, which may provide a convenient and rapid screening method for cardiac events at point-of-care.

Nanobiosensors for Detection of Cardiovascular Disorders

Nanobiosensors can be electronically gated to respond to the binding of a single molecule. Prototype sensors have demonstrated detection of nucleic acids, proteins, and ions. These sensors can operate in the liquid or gas phase, opening up an enormous variety of downstream applications. The detection schemes use inexpensive low voltage measurement schemes and detect binding events directly so there is no need for costly, complicated and time-consuming labeling chemistries such as fluorescent dyes or the use of bulky and expensive optical detection systems. As a result, these sensors are inexpensive to manufacture and portable. It may even be possible to develop implantable detection and monitoring devices for cardiovascular disorders based on these detectors.

Use of Magnetic NPs as MRI Contrast Agents for Cardiac Imaging

Magnetic nanoparticles (MNPs) have been used as contrast agent for MRI and have refined molecular imaging. Targeted imaging of vascular inflammation or thrombosis may enable improved risk assessment of atherosclerosis by detecting plaques at high risk of acute complications (Saraste et al. 2009). Cell death in the heart can be imaged in vivo by using annexin-labeled MNPs, particularly AnxCLIO-Cy5.5 (Chen et al. 2011). Experimental studies have shown the feasibility of combination of diagnosis and therapy using MNPs. In a study on mice, MNPs conjugated with plasmid DNA expressing enhanced green fluorescent protein and coated with chitosan were injected into tail vein and directed to the heart by means of an external magnet without the need to functionalize the NPs, and their location was confirmed by fluorescent imaging (Kumar et al. 2010). This approach requires further investigations before clinical applications can be considered.

Perfluorocarbon NPs for Combining Diagnosis with Therapy in Cardiology

Perfluorocarbon (PFC) nanoparticles provide an opportunity for combining molecular imaging and local drug delivery in cardiovascular disorders. Ligands such as MAbs and peptides can be cross-linked to the outer surface of PFCs to enable active targeting to biomarkers expressed within the vasculature. PFC nanoparticles are naturally constrained by size to the circulation, which minimizes unintended binding to extravascular, nontarget tissues expressing similar epitopes. Moreover, their prolonged circulatory half-life of approximately 5 h allows saturation of receptors without addition of PEG or lipid surfactant polymerization. The utility of targeted PFC nanoparticles has been demonstrated for a variety of applications in animal models and phantoms, including the diagnosis of ruptured plaque, the quantification and antiangiogenic treatment of atherosclerotic plaque, and the localization and delivery of antirestenotic therapy following angioplasty (Lanza et al. 2006).

Cardiac Monitoring in Sleep Apnea

Because sleep apnea is a cause of irregular heartbeat, hypertension, heart attack, and stroke, it is important that patients be diagnosed and treated before these highly deleterious sequelae occur. For patients suspected of experiencing sleep apnea, in vivo sensors could constantly monitor blood concentrations of oxygen and cardiac function to detect problems during sleep. In addition, cardio-specific antibodies tagged with nanoparticles may allow physicians to visualize heart movement while a patient experiences sleep apnea to determine both short- and long-term effects of apnea on cardiac function.

Detection and Treatment of Atherosclerotic Plaques in the Arteries

A key feature of the atherosclerotic process is the angiogenic expansion of the vasa vasorum in the adventitia, which extends into the thickening intimal layer of the atheroma in concert with other neovessels originating from the primary arterial lumen. Magnetic resonance molecular imaging of focal angiogenesis with integrin-targeted paramagnetic contrast agents has been reported with PFC nanoparticles and liposomes. Site-targeted PFC nanoparticles also offer the opportunity for local drug delivery in combination with molecular imaging.

The diagnosis and treatment of unstable plaque is an area in which nanotechnology could have an immediate impact. Fibrin-specific PFC nanoparticles may allow the detection and quantification of unstable plaque in susceptible patients, which may be an important feature of future strategies to prevent heart attacks or stroke.

Research is under way using probes targeted to plaque components for noninvasive detection of patients at risk. In an extension of this approach, targeted nanoparticles, multifunctional macromolecules, or nanotechnology-based devices could deliver therapy to a specific site, localized drug release being achieved either passively (by proximity alone) or actively (through supply of energy as ultrasound, near-infrared, or magnetic field). Targeted nanoparticles or devices could also stabilize vulnerable plaque by removing material, e.g., oxidized low-density lipoproteins. Devices able to attach to unstable plaques and warn patients and emergency medical services of plaque rupture would facilitate timely medical intervention.

Monitoring for Disorders of Blood Coagulation

Patients would benefit greatly from nanotechnology devices that could monitor the body for the onset of thrombotic or hemorrhagic events. Multifunctional devices could detect events, transmit real-time biologic data externally, and deliver anticoagulants or clotting factors to buy critical time.

A gold nanoparticle-based simple assay has been described that enables the visual detection of a protease (Guarise et al. 2006). The method takes advantage of the high molar absorptivity of the plasmon band of gold colloids and is based on the color change of their solution when treated with dithiols. Contrary to the native ones, cleaved peptides are unable to induce nanoparticles aggregation; hence, the color of the solution does not change. The assay was used to detect two proteases: thrombin (involved in blood coagulation and thrombosis) and lethal factor (an enzyme component of the toxin produced by *Bacillus anthracis*). The sensitivity of this nanoparticle-based assay is in the low nanomolar range.

Controlled Delivery of Nanoparticles to Injured Vasculature

Optimal size of nanoparticles designed for systemic delivery is approximately 50–150 nm, but this size range confers a high surface area-to-volume ratio, which results in fast diffusive drug release. Spatial control has been achieved by biopanning a phage library to discover materials that target abundant vascular antigens exposed in disease (Chan et al. 2010). Temporal control is achieved by designing 60-nm hybrid nanoparticles with a lipid shell interface surrounding a polymer core, which is loaded with slow-eluting conjugates of paclitaxel for controlled ester hydrolysis and drug release over approximately 12 days. The nanoparticles inhibit human aortic smooth muscle cell proliferation in vitro and showed greater in vivo vascular retention during percutaneous angioplasty as compared to nontargeted controls. This nanoparticle technology may potentially be used toward the treatment of injured vasculature.

IGF-1 Delivery by Nanofibers to Improve Cell Therapy for Myocardial Infarction

Strategies for cardiac repair include injection of cells, but these approaches have been hampered by poor cell engraftment, survival, and differentiation. To address these shortcomings for the purpose of improving cardiac function after injury, a self-assembling peptide nanofiber was designed for prolonged delivery of insulin-like growth factor 1 (IGF-1), a cardiomyocyte growth and differentiation factor, to the myocardium, using a "biotin sandwich" approach (Davis et al. 2006). Biotinylated IGF-1 was complexed with streptavidin and then bound to biotinylated self-assembling peptides. This biotin sandwich strategy enabled binding of IGF-1 but did not prevent self-assembly of the peptides into nanofibers within the myocardium. IGF-1 that was bound to peptide nanofibers activated Akt, decreased activation of caspase-3, and increased expression of cardiac troponin I in cardiomyocytes. In studies on rats, cell therapy with IGF-1 delivery by biotinylated nanofibers improved systolic function after experimental myocardial infarction. This nanobiotechnology approach has the potential to improve the results of cell therapy for myocardial infarction, which is in clinical trials currently.

Injectable Peptide Nanofibers for Myocardial Ischemia

Endothelial cells can protect cardiomyocytes from injury through platelet-derived growth factor (PDGF)-BB signaling. PDGF-BB induces cardiomyocyte Akt phosphorylation in a time- and dose-dependent manner and prevents apoptosis via PI3K/Akt signaling. An experimental study in rats using injectable self-assembling peptide nanofibers, which bound PDGF-BB in vitro, demonstrated sustained delivery of PDGF-BB to the myocardium at the injected sites for 14 days (Hsieh et al. 2006). This blinded and randomized rat study showed that injecting nanofibers with PDGF-BB, but not nanofibers or PDGF-BB alone, decreased cardiomyocyte death and preserved systolic function after myocardial infarction. A separate blinded and randomized study showed that PDGF-BB delivered with nanofibers decreased infarct size after ischemia/reperfusion. PDGF-BB with nanofibers induced PDGFR-β and Akt phosphorylation in cardiomyocytes in vivo. These data demonstrate that PDGF-BB signaling and in vitro finding can be translated into an effective in vivo method of protecting myocardium after infarction. Furthermore, this study shows that injectable nanofibers allow precise and sustained delivery of proteins to the myocardium with potential therapeutic benefits.

Liposomal Nanodevices for Targeted Cardiovascular Drug Delivery

High-affinity ligand-receptor interactions have been exploited in the design and engineering of targeting systems that use a liposomal nanodevice for site-specific cardiovascular drug delivery. An example of application is atherothrombosis, a condition in which platelet activation/adhesion/aggregation is closely associated with vascular thrombotic events. Therefore, the majority of antithrombotic therapies have focused on drugs that impede platelet-activation pathways or block ligand-binding platelet integrins. In spite of reasonable clinical efficacy of these therapies, the magic bullet, a single drug and delivery system that selectively targets pathologically thrombotic environment without affecting hemostatic balance, remains elusive. The use of anti-integrin/anticoagulant/anti-inflammatory drugs in conjunction might be necessary to treat the multifactorial nature of pathological thrombogenesis. For this purpose, a nanoscale device that can carry such a combination selectively to a thrombotic site is being developed at the Department of Biomedical Engineering of Case Western Reserve University (Cleveland, OH). The liposomal nanodevice surface is modified by RGD (arginine-glycine-aspartic acid) motifs that specifically target and bind activated platelets by virtue of the high-affinity interaction between the RGD motif and the integrin GPIIb-IIIa expressed on active platelets, potentially acting as a thrombus-targeted vector. The ability of such liposomes to compete with native ligand fibrinogen in specifically binding activated platelets has been accomplished using both in vitro and in vivo approaches. The results demonstrate feasibility of using liposomes as platelet-targeted devices for delivery of cardiovascular therapeutics. By utilizing a library of synthetic peptide/peptidomimetic ligands having binding affinity toward specific receptors expressed in cardiovascular biology, it is possible to manipulate the liposome surface modification and hence dictate targeting specificity and affinity of the liposomal nanodevices.

Low-Molecular-Weight-Heparin-Loaded Polymeric Nanoparticles

Low-molecular-weight-heparin (LMWH) nanoparticles are available as potential oral heparin carriers. The nanoparticles are formulated using an ultrasound probe by water-in-oil-in-water emulsification and solvent evaporation with polymers. The mean diameter of LMWH-loaded nanoparticles ranges from 240 to 490 nm and is dependent on the reduced viscosity of the polymeric organic solution. The highest encapsulation efficiencies are observed when Eudragit polymers are used in the composition of the polymeric matrix. The in vitro biological activity of released LMWH, determined by the antifactor Xa activity with a chromogenic substrate, is preserved after the encapsulation process, making these nanoparticles good candidates for oral administration.

Nanoparticles for Cardiovascular Imaging and Targeted Drug Delivery

The potential dual use of nanoparticles for both imaging and site-targeted delivery of therapeutic agents to cardiovascular disease offers great promise for individualizing therapeutics. Image-based therapeutics with site-selective agents should enable verification that the drug is reaching the intended target and a molecular effect is occurring. Experimental studies have shown that binding of paclitaxel to smooth muscle cells in culture has no effect in altering the growth characteristics of the cells. If paclitaxel-loaded nanoparticles are applied to the cells, however, specific binding elicits a substantial reduction in smooth muscle cell proliferation, indicating that selective targeting may be a requirement for effective drug delivery for in this situation. Similar behavior has been demonstrated for doxorubicin containing particles. Intravenous delivery of fumagillin (an antiangiogenic agent)-loaded nanoparticles targeted to αvβ3-integrin epitopes on vasa vasorum in growing plaques results in marked inhibition of plaque angiogenesis in cholesterol-fed rabbits. The unique mechanism of drug delivery for highly lipophilic agents such as paclitaxel contained within emulsions depends on close apposition between the nanoparticle carrier and the targeted cell membrane and has been described as "contact-facilitated drug delivery." In contrast to liposomal drug delivery (generally requiring endocytosis), the mechanism of drug transport in this case involves lipid exchange or lipid mixing between the emulsion vesicle and the targeted cell membrane, which depends on the extent and frequency of contact between two lipidic surfaces. The rate of lipid exchange and drug delivery can be greatly increased by the application of clinically safe levels of ultrasound energy that increase the propensity for fusion or enhanced contact between the nanoparticles and the targeted cell membrane.

The combination of targeted drug delivery and molecular imaging with MRI has the potential to enable serial characterization of the molecular epitope expression based on imaging readouts. Monitoring and confirmation of therapeutic efficacy of the therapeutic agents at the targeted site would facilitate personalized medical regimens.

Nanofiber-Based Scaffolds with Drug-Release Properties

Electrospinning is a versatile technique that enables the development of nanofiber-based scaffolds, from a variety of polymers that may have drug-release properties. Using nanofibers, it is now possible to produce biomimetic scaffolds that can mimic the extracellular matrix for tissue engineering (Ashammakhi et al. 2009). Nanofibers can guide cell growth along their direction. Combining factors like fiber diameter, alignment, and chemicals offers new ways to control tissue engineering. In vivo evaluation of nanomats included their degradation, tissue reactions, and engineering

of specific tissues. New advances made in electrospinning, especially in drug delivery, support the massive potential of these nanobiomaterials. Nevertheless, there is already at least one product based on electrospun nanofibers with drug-release properties in a phase III clinical trial, for wound dressing. Hopefully, clinical applications in tissue engineering will follow to enhance the success of regenerative therapies.

NP-Based Systemic Drug Delivery to Prevent Cardiotoxicity

Nanotechnology can have a beneficial effect on cardiovascular health by reducing cardiotoxicity of drugs used to treat noncardiac diseases. Use of halofantrine, an antimalarial drug for treatment of multidrug-resistant malaria, is limited by prolongation of the QT interval (the time between the Q wave and the end of the T wave) as seen on ECG, which can result in bradycardia and hypotension. By encapsulating the drug in polycaprolactone nanocapsules, halofantrine was administered in mice with blunting of the cardiotoxic effects of the drug (Leite et al. 2007). Nanoparticle encapsulation also shows promise for reduction of cardiotoxicity of other drugs. For example, administration of the anticancer drug doxorubicin is limited by cardiotoxicity. However, doxorubicin packaged into 100 nm pegylated liposomes shows comparable efficacy but reduced cardiotoxicity.

Nanotechnology-Based Therapeutics for Cardiovascular Diseases

Nanolipoblockers for Atherosclerotic Arterial Plaques

Nanoscale particles can be synthetically designed to potentially intervene in lipoprotein matrix retention and lipoprotein uptake in cells – processes central to atherosclerosis. These micelles can be engineered to present varying levels of anionic chemistry, which is a key mechanism to induce differential retentivity of low-density lipoproteins (LDLs). Rutgers University scientists have reported on lipoprotein interactions of nanoscale micelles self-assembled from amphiphilic scorpion-like macromolecules based on a lauryl chloride-mucic acid hydrophobic backbone and poly(ethylene glycol) shell. They have used nanoengineered molecules called nanolipoblockers (NLBs) to attack atherosclerotic plaques due to raised levels of LDLs (Chnari et al. 2006). Their approach contrasts with statin drug therapy, which aims to reduce the amount of LDL throughout the body. NLPs compete with oxidized LDLs for a macrophage's attention. The NLBs bind to receptor sites on macrophages, cutting the accumulation of oxidized LDL by as much as 75 %.

Nanotechnology Approach to the Vulnerable Plaque as Cause of Cardiac Arrest

Recent studies have shown that plaque exists in two modes: nonvulnerable and vulnerable. The latter is the probable cause of death in sudden cardiac arrest. Blood passing through an artery exerts a shearing force and can cause vulnerable plaque to rupture, which often leads to occlusion and myocardial infarction. Approximately 60–80 % of sudden cardiac deaths can be attributed to the physical rupture of vulnerable plaque.

There is currently no satisfactory solution to the problem of vulnerable plaque, but it will be tackled by a "Program of Excellence in Nanotechnology" by the National Heart, Lung, and Blood Institute of the NIH. In concert with the NIH's strategy to accelerate progress in medical research through innovative technology and interdisciplinary research, cardiac disease was chosen as the focus of the National Heart, Lung, and Blood Institute's Program of Excellence in Nanotechnology. The program will be a partnership of 25 scientists from the Burnham Institute (La Jolla, CA); University of California, Santa Barbara; and The Scripps Research Institute (San Diego, CA) that will design nanotechnologies to detect, monitor, treat, and eliminate "vulnerable" plaques. By focusing on devising nanodevices, machines at the molecular level, the scientists at these institutions will specifically target vulnerable plaque. It is hoped that this work will lead to useful diagnostic and therapeutic strategies for those suffering from this form of cardiac disease. The project team will work on three innovative solutions to combat vulnerable plaque:

- Building delivery vehicles that can be used to transport drugs and nanodevices to sites of vulnerable plaque
- Designing a series of self-assembling polymers that can be used as molecular nanostents to physically stabilize vulnerable plaque
- Creating nanomachines comprised of human proteins linked to synthetic nanodevices for the purpose of sensing and responding to vulnerable plaque

Nanotechnology for Regeneration of the Cardiovascular System

Nanotechnology may facilitate repair and replacement of blood vessels, myocardium and myocardial valves. It also may be used to stimulate regenerative processes such as therapeutic angiogenesis for ischemic heart disease. Cellular function is integrally related to morphology, so the ability to control cell shape in tissue engineering is essential to ensure proper cellular function in final products. Precisely constructed nanoscaffolds and microscaffolds are needed to guide tissue repair and replacement in blood vessels and organs. Nanofiber meshes may enable vascular grafts with superior mechanical properties to avoid patency problems

common in synthetic grafts, particularly small-diameter grafts. Cytokines, growth factors, and angiogenic factors can be encapsulated in biodegradable microparticles or nanoparticles and embedded in tissue scaffolds and substrates to enhance tissue regeneration. Scaffolds capable of mimicking cellular matrices should be able to stimulate the growth of new heart tissue and direct revascularization.

Nanostructures promote formation of blood vessels and bolster cardiovascular function after heart attack. Scientists at the Institute of Bionanotechnology in Medicine at Northwestern University (Evanston, Ill) have shown that injecting nanoparticles into the hearts of mice that suffered heart attacks helped restore cardiovascular function in these animals. The finding is an important research advance that one day could help rapidly restore cardiovascular function in people who have heart disease. The self-assembling nanoparticles – made from naturally occurring polysaccharides and molecules known as peptide amphiphiles – boost chemical signals to nearby cells that induce formation of new blood vessels, and this may be the mechanism through which they restore cardiovascular function. One month following injection, the hearts of the treated mice were capable of contracting and pumping blood almost as well as healthy mice. In contrast, the hearts of untreated mice contracted about 50 % less than normal.

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Nanotechnology-Based Stents

A coronary stent is a tiny expandable mesh tube made of medical grade stainless steel. A stent is delivered on a balloon catheter and implanted in the coronary artery after balloon angioplasty to help keep the artery open. After the plaque is compressed against the arterial wall, the stent is fully expanded into position, thereby acting as miniature “scaffolding” for the artery. The balloon is then deflated and removed and the coronary stent is left behind in the patient’s blood vessel. It may be necessary to place more than one stent, depending on the length of the blockage. The inside lining of the artery eventually heals around the stent. Technical advances are providing the development of improved materials for coating of DES. Nanomaterials are the most prominent among these.

Restenosis After Percutaneous Coronary Angioplasty

Restenosis after percutaneous coronary intervention continues to be a serious problem in clinical cardiology. Advances in nanoparticle technology have enabled the delivery of NK911, an antiproliferative drug, selectively to the balloon-injured artery for a longer time (Uwatoku et al. 2003). NK911 is a core-shell nanoparticle of PEG-based block copolymer encapsulating doxorubicin. It accumulates in vascular lesions with increased permeability. In a balloon injury model of the rat carotid artery, intravenous administration of NK911 significantly inhibited the neointimal formation. The effect of NK911 was due to inhibition of vascular smooth muscle proliferation but not to enhancement of apoptosis or inhibition of inflammatory cell recruitment. NK911 was well tolerated without any adverse systemic effects. These results suggest that nanoparticle technology is a promising and safe approach to target vascular lesions with increased permeability for the prevention of restenosis after balloon injury. Coroxane™ (Abraxis), a nanoparticulate microtubule stabilizer, is in phase II clinical trials in conjunction with angioplasty/stents to prevent arterial restenosis.

Biomedical engineers at Purdue University (Lafayette, IN) have shown that vascular stents used to repair arteries might perform better if their surfaces contained "nanobumps" that mimic tiny features found in living tissues. The stents, which are made of titanium and other metals, enable the arteries to grow new tissue after vessel-clogging plaque deposits have been removed. A major problem, however, is that the body often perceives the metal devices as foreign invaders, hindering endothelial cells from attaching to the scaffolding and prompting the creation of scar tissue, which can build up inside blood vessels and interfere with blood flow. If a stent does not attach firmly, it can become loose, and parts of it will actually break off and go down the bloodstream. There is need for new materials that cause the endothelial cells to attach better to these stents without creating as much dangerous scar tissue. The researchers tested disks of titanium containing surface bumps about as wide as 100 nm. The metals used to make conventional stents have features about 10 times larger or none at all. The nanometer-scale bumps mimic surface features of proteins and natural tissues, prompting cells to stick better. Ideally endothelial cells should quickly attach to stents and form a coating only one cell layer thick. The researchers found that nearly three times as many cells stuck to the disks containing the nanobumps, as compared to ordinary titanium. Further research is planned that will replace the titanium disks with tube-shaped pieces of the nano-featured metal, which will resemble the actual shape of real stents.

Currently available stents have problems with imaging within the stent structure, where potential restenosis can occur. Biophan Technologies Inc. has two solutions for stent visibility: a thin-film nanomagnetic particle-coating solution and an anti-antenna solution. These solutions enable the noninvasive, MRI-based, imaging of

these devices which today can only be accomplished through more complicated invasive procedures. These approaches will become an important part of the rapidly growing worldwide market for stents and vascular implants.

By using antiproliferative compounds that elute from the surface of a stent, the latest generation of stents has enabled a significant reduction in restenosis rates, i.e., when there is a renarrowing of the vessel after stent implantation. Nanocarrier-based delivery presents a viable alternative to the current stent-based therapies (Brito and Amiji 2007; Feng et al. 2007; Margolis et al. 2007).

Drugs Encapsulated in Biodegradable Nanoparticles

Local delivery of antiproliferative drugs encapsulated in biodegradable nanoparticles has shown promise as an experimental strategy for preventing restenosis development. A novel PDGFR-β-specific tyrphostin, AGL-2043 (Calbiochem), was formulated in polylactide-based nanoparticles and was administered intraluminally to the wall of balloon-injured rat carotid and stented pig coronary arteries (Banai et al. 2005). The antiproliferative effect of nanoencapsulated tyrphostin was found to be considerably higher than that of surface-adsorbed drug. In the pig model, intramural delivery of AGL-2043 resulted in reduced in-stent neointima formation in the coronary arteries as compared to control despite similar degrees of wall injury. The results of this study suggest that locally delivered tyrphostin AGL-2043 formulated in biodegradable nanoparticles may be applicable for antirestenotic therapy independent of stent design or type of injury.

Magnetic Nanoparticle–Coated DES

Biophan Technologies' drug delivery technology (Fig. 10.1), based on tuning magnetic nanoparticles (MNPs) to resonate at a specific frequency, led to their use for selective control of drug release. This technology can be used for reloading drug-eluting coatings for surface elution on demand is active in contrast to the passive drug-eluting polymer coatings. It provides a physician better control over the patient's treatment. Currently, many cardiovascular experts predict the next generation of DES will be comprised of a biocompatible, biodegradable, resorbable material with the strength to acutely open and maintain the confirmation of a vessel. The advantage is that they gradually dissolve while delivering the drug. At the end of a predetermined period, nothing is left at the site where it was introduced.

Magnetic Nanoparticles Encapsulating Paclitaxel Targeted to Stents

Because current DESs lack the capacity for adjustment of the drug dose and release kinetics to the disease status of the treated vessel, attempts have been made to address these limitations by a strategy combining magnetic targeting via a uniform-field-induced magnetization effect and a biocompatible magnetic nanoparticle

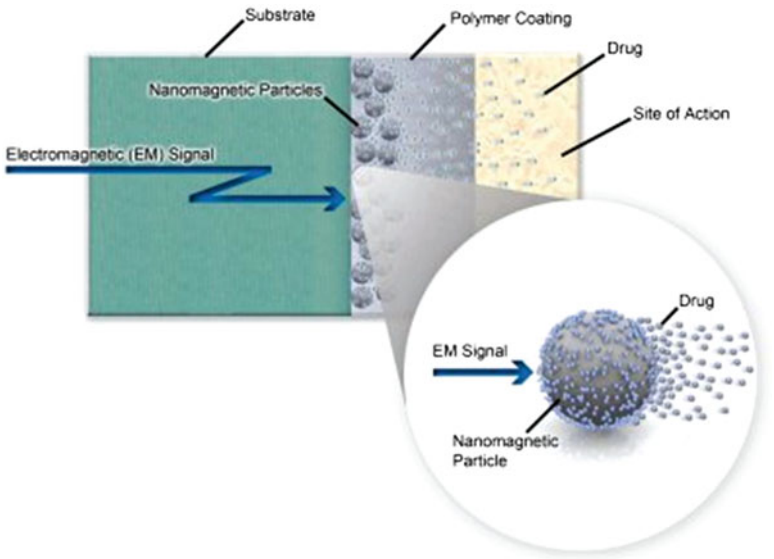

Fig. 10.1 Magnetic nanoparticle–coated stent (Reproduced by permission of Biophan Technologies Inc.)

(MNP) formulation designed for efficient entrapment and delivery of paclitaxel (PTX). Magnetic treatment of cultured arterial smooth muscle cells with PTX-loaded MNPs was shown to inhibit cell growth significantly as compared to non-magnetic conditions (Chorny et al. 2010). Furthermore, significantly higher localization rates of locally delivered MNPs to stented arteries were achieved with uniform-field-controlled targeting compared to nonmagnetic controls in the rat carotid stenting model. The arterial tissue levels of stent-targeted MNPs remained four- to tenfold higher in magnetically treated animals vs. control over 5 days post-delivery. The enhanced retention of MNPs at target sites due to the uniform-field-induced magnetization effect resulted in a significant inhibition of in-stent restenosis with a relatively low dose of MNP-encapsulated PTX. This study demonstrates the feasibility of site-specific drug delivery to implanted magnetizable stents by uniform-field-controlled targeting of MNPs with efficacy for in-stent restenosis.

Nanocoated DES

MIV Therapeutics Inc has developed unique coating technologies that utilize hydroxyapatite (HAp) for application on medical devices and drug delivery systems. The lead product in development is a HAp-coated coronary stent with a

nanofilm coating. In 2006, the results of an independently conducted 4-week porcine study, performed by the Department of Cardiology, Thoraxcenter, Erasmus University Medical Center in the Netherlands, indicated that three variations of MIV's polymer-free drug-eluting coatings were at least as effective as or better than Cypher (Johnson & Johnson). The study concluded that MIV's HAp coating, with or without drugs, demonstrated highly promising performance. A pilot clinical trial was launched in 2007, and the first HAp-coated was implanted at the Institute Dante Pazzanese of Cardiology in Sao Paulo, Brazil.

ElectroNanospray™ formulation technology (Nanocopoeia Inc.) produces precise, ultrapure nanoparticles. Particle sizes can be designed from 2 to 200 nm. The device is capable of applying a coating to the particles in a single process step, producing a drug-loaded core. Competitive processes to produce nanoparticles using wet milling and super critical fluid are inherently limited in their ability to produce consistently pure particles within a specified size range and distribution. ElectroNanospray™ technology provides a novel approach for applying challenging materials to the surfaces of medical devices. This process can generate both single- and multiple-phase coatings and apply these with tight control to small, complex surfaces. ElectroNanospray™ process is being developed for applying nanoparticle-based drug-eluting coatings to coronary stents.

Debiotech SA in collaboration with the Laboratory of Powder Technology at Ecole Polytechnique Fédérale de Lausanne (Lausanne, Switzerland) is developing a new type of structured ceramic coatings for drug-eluting stents and other implants. Ceramics offer unique properties compared to polymers. Polymers dissolve over time and residues provoke inflammation, whereas ceramic is stable and inert when in contact with living tissue. With this coating, one can combine an active release of drug during the first weeks after implantation with the long-term stability of the ceramic. Nanostructured ceramics provide novel properties to biomaterials which are not attainable with other materials. The challenge in this project is to process nanosized ceramic powders to reach unique surface structures, which show a controlled porosity over a size range of 2,000 times between the smallest and largest pore. Based on results of fundamental research activities in the field of ordered arrangement of nanosized particles at surfaces, the knowledge of processing particles smaller than 10 nm at large scale has been established as a key competence to achieve that goal.

Nanopores to Enhance Compatibility of DES

Scientists at the Forschungszentrum Dresden-Rossendorf in Germany have developed an innovative method to create a large number of nanopores on the surface of stainless steel. Bombarding the surface of a stent from all sides with a high dose of noble gas ions generates a scaffold of nanopores in the material below the surface. The desired porosity can be precisely engineered by tuning the ion energy, the flux, and the temperature during the process. A larger amount of the highly

effective drugs can be deposited on the enlarged noble metal surface, due to this nanoporous structure, which enhances the biocompatibility of the implants in the human body. Thus, this treatment results in the release of drugs over a longer period of time. This method is currently being assessed as a platform technology for the next generation of DES by the Boston Scientific Corporation. The objective of this research collaboration is to further develop this technique for commercialization.