POLYMER-FREE DRUG DELIVERY FROM STENTS

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Background

Currently, over 60 million people in the US suffer from atherosclerosis, a disease that causes over 450,000 deaths and 100,000 limb amputations here each year. Vascular stents provide a means of significantly improving the quality of life for patients suffering from this disease. Stents can be used to quickly eliminate angina and intermittent claudication and have also been shown to provide a reliable means of avoiding limb amputations as well. Atherosclerosis is a disease that worsens with age and stenting therefore represents a key medical treatment to ensure that the additional years of life attained now by the general population as a result of improved medical care are productive and of high quality. Consequently, the demand for stenting has grown steadily for the past two decades and this trend is very likely to continue. The number of drug eluting stents (DES) implanted annually is expected to reach 4.5 million worldwide by 2010 and sales for coronary stents alone is expected to reach $7.2 billion worldwide by 2012.

Bare metal stents (BMS) have suffered from unacceptably high rates of restenosis (> 30%) in coronary arteries[1,2] and 50% in superficial femoral[3] and infrapopliteal[4,5] arteries. Polymer coated drug eluting stents (PDES) dramatically reduce the rate of restenosis for coronary stents to less than 10%[6] but have been associated with fatal side effects. There is an urgent need for a new DES platform that minimizes restenosis without biocompatibility problems. This project will develop a safe and effective polymer-free drug eluting coronary stent.

Currently all four FDA approved drug eluting coronary stents use permanent polymer coatings to deliver anti-restenosis drugs. However, a number of studies since 2004 have shown that these PDES significantly increase the risk of thrombus formation.[7,8,9] After six months, the risk of death with a PDES increases at the rate of approximately 0.5% per year out to more than three years.[10,11] Pathologic studies of patients who have died from late PDES thrombosis have shown poor endothelialization[12,13] of the stent struts, increased platelet deposition[14], aneurysms[15], and stent malapposition.[16,17] These studies show that tissue adjacent to the stent struts is inflamed and that cell death is the cause for malapposition.[18] It is well known that polymers can induce local hypersensitivity reactions that can lead to tissue inflammation and an increase in platelet activation.[19] The role of the drug in the hypersensitivity process appears to be minimal since the observed hypersensitivity involves T cells that are actually suppressed by antirestenosis drugs.[20] As a result of these findings, it now appears that the long term presence of polymer is the root cause for the increased risk of late stent thrombosis.[21]

More recently, drug eluting stents with a biodegradable polymer coating (BPDES) have been developed in an attempt to avoid the problems seen with permanent polymers. Clinical studies with these stents have now reached two years and the results show there is no safety benefit to

replacing the permanent polymer with a biodegradable polymer.[22,23] Even relatively short term presence of polymer causes hypersensitivity reactions. These findings also cast doubt on the safety of the highly sought after bioabsorbable stent platform.

A polymer-free DES (PFDES) has the important advantage that it is unlikely to induce hypersensitivity reactions. Although PFDES release kinetics will likely be different from those of PDES, this may not represent a problem. Experimental and computation work has shown that pharmacokinetics (PK) plays perhaps the dominate role in determining the evolution of drug-tissue distribution which in turn is the primary determinant of antirestenosis efficacy.[24] There are several PFDES in development or clinical trials now.[25,26] The Nile Pax, Translumina Yukon and Biosensors Biofreedom stents utilize a pure drug film on the stent surface. A major problem with this approach is drug delamination from the stent during deployment which makes it impossible to ensure correct dosage. In contrast, reservoir type PFDES can protect the solid drug during deployment. Macroscopic wells (holes or grooves) are used on the Cordis Coner, Sorin Janus Flex and Medtronic Drug Filled stents. A significant problem with this approach is that it produces a highly concentrated flux of drug over a small area of tissue. In contrast, nanoporous coatings can provide uniform release over the entire stent-tissue contact area. Setagon and MIV Therapeutics have both developed nanoporous PFDES but both have brittle coatings that can crack and delaminate during deployment. Additionally, these porous coatings are characterized by closed, non-interconnected tortuous pores that are difficult or impossible to load with drug.

a)

b)

Figure 1. SEM images for a 7.5 μm thick tantalum porous columnar coating on SS. (a) top down and (b) cross section. Ta columns are approximately 250 nm wide.

The Isoflux Approach

Isoflux has developed a polymer-free DES that utilizes a nanoporous and radiopaque metallic coating with a structure that provides a protective reservoir for drug and is also free of common film failure modes such as cracking and delamination from the stent. This polymer-free approach completely avoids the problem of long term hypersensitivity reactions induced by polymers and the associated increased risk of late and very late stent thrombosis. Work in our laboratory has demonstrated that our unique cylindrical magnetron sputtering equipment can be used to produce tantalum and chromium coatings consisting individual columns that are separated by a continuous pore space and that have excellent adhesion to stainless steel and Nitinol. Figure 1 shows SEM images of tantalum porous columnar coatings. The columnar structure does not develop tensile stress during stent expansion since the columns can move relative to each other. As a result, the coating thickness need

not be limited to avoid film failure. We have demonstrated the ability to produce coatings up to 30 microns thick without delamination. The coating can be applied only to selected areas of the stent if desired (e.g., abluminal only).

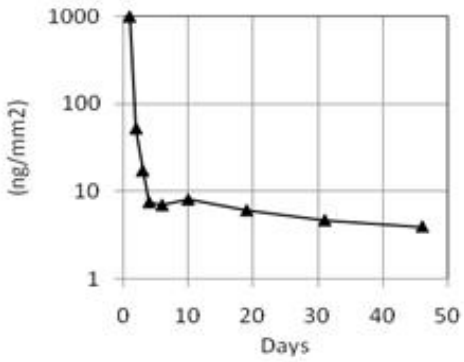

Figure 2. Rapamycin release from a 20 μm Cr porous columnar coating into PBS at 37 C.

The porosity of the coatings we have made ranges from 15 to 25%. A number of controllable factors such as materials used and sputtering conditions interact to determine the coating morphology and the work planned for this project will provide an understanding of these fundamental interactions. The pore volume within the coating provides a drug load capacity that can exceed the drug loads of current FDA approved PDES by a factor of two or more. Additionally, the pores are completely open and fully interconnected in contrast to all other porous coatings developed so far for a PFDES. As a result, it is expected that efficient drug filling of the pore space can be readily achieved by standard processes such as dipping or spraying and without the complicated additional techniques needed to load other porous structures.[27]

Furthermore, in vitro drug elution studies we have performed show two distinct phases of release. Figure 2 shows a plot of in vitro rapamycin release from a porous columnar chromium coating. The initial rapid release is likely governed by drug dissolution while the slower long term release is likely a result of desorption of the final monolayer of drug. Medically significant amounts of drug can be contained in a monolayer because of the extremely high surface area of the coating. The relative amount of drug release in each phase should depend on the surface area of exposed drug film. Loading processes that result in drug films that line the sides of the columns will likely elute much faster than drug films that fill the pores completely. This project will enable an understanding of these effects so that the character of the release can be modified if necessary. Finally, if high atomic number metals are used to make the porous coating, the radiopacity of the entire stent framework can be significantly enhanced as well. Figure 3 shows the radiopacity enhancement produced by a 10 μm coating of tantalum on a Nitinol stent. Although the focus here is on the development of a coronary stent, the results are directly applicable to the development of peripheral stents and non-vascular stents for tissue growth suppression and cancer therapy.[28]

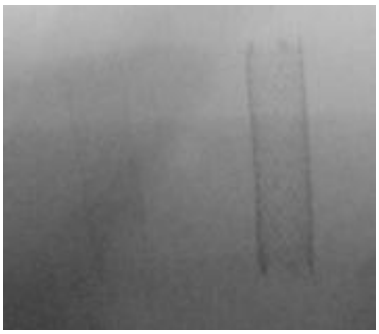

Figure 3. X-ray image of a bare Nitinol stent on the left (faint) and a Nitinol stent with a 10 μm coating of Ta.

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