The introduction and refinement of stenting as a means for catheter-based coronary revascularization has rapidly changed the face of interventional cardiology. At many leading centers, 60-70% of all percutaneous coronary interventions now utilize stenting. The relatively rapid acceptance and increasingly widespread use of stents has been driven by an improvement in the predictability of intervention with lessened acute and subacute closure, and convincing randomized data (at least with the Palmaz-Schatz stent) of improved intermediate and long-term clinical outcomes.\textsuperscript{1-3}

Although stenting has clearly made a substantial impact in improving the restenosis problem after angioplasty, in stent restenosis remains a problem particularly after stenting longer lesions, smaller vessels, ostial lesions and saphenous vein grafts. In these subsets clinically important restenosis still occurs in 25-45%. This paper will address the rationale, development, in vitro and in vivo data relevant to the development of a beta-particle (electron) emitting radioisotope stent intended to further decrease restenosis after stenting.

**Mechanism of Restenosis: Stenting versus Balloon Angioplasty.** Figure 1 shows a photomicrograph of a Palmaz-Schatz stent 7 months after implantation in the left circumflex coronary artery of a cardiac transplant patient with accelerated transplant atherosclerosis. The patient received a second heart transplant, and we were able to examine the stented segment. One can appreciate a tremendous volume of neointimal hyperplasia within the lumen, inside the stent. The stent remains well expanded, without evidence of extrinsic stent compression. This finding is consistent with recently presented intravascular ultrasound data\textsuperscript{4} following human coronary stent implantation. This picture contrasts with the recent IVUS data regarding the mechanisms of restenosis after balloon angioplasty and directional atherectomy.\textsuperscript{5,6} In those patients it is becoming increasingly clear that a substantial proportion of late luminal loss is due to late constriction ("unfavorable remodeling") of the treated segment, with a more modest contribution from neointimal hyperplasia. Thus, the impact of stents upon improved long-term outcome is in large part related to the scaffolding effect of the stent which prevents late constriction of the segment. Interestingly, late loss secondary to neointimal hyperplasia appears to be significantly increased after stenting as compared to balloon angioplasty alone.\textsuperscript{2} This important observation leads one to the logical next step in the prevention of restenosis; namely the

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inhibition of the neointimal hyperplastic response after stenting. If one extrapolates from the late luminal loss data from the Benestent study one can determine that as little as a 20% inhibition of neointimal hyperplasia after stenting would yield a reduction in angiographic restenosis from 22% to approximately 8%. A 50% inhibition would theoretically yield a 0% angiographic restenosis rate. Thus, a modest reduction in the neointimal hyperplastic response after stenting can result in amplification of the benefits of stenting and should lead to a very low incidence of restenosis. The concept presented below is the use of a stent to provide the scaffolding effect, described above, with the additional use of the stent as a platform to locally deliver low–dose beta particle irradiation to try to modulate and inhibit smooth muscle cell proliferation after stent implantation.

**Design Features of a Radioisotope Stent.**

We believe that beta–particles (free electrons) may provide an ideal type of radiation when using a stent as a radiation delivery platform. Beta–particles have the major advantage, as compared to gamma irradiation, of providing truly localized irradiation. The maximum range of beta–particle irradiation in tissue is approximately 7 mm with 95% of the radiation dose being absorbed within 3.5 mm from the stent. Phosphorous 32 ($^{32}$P) is an excellent radioisotope choice for this application since it is a pure beta–particle emitter (no gamma), has relatively high energy beta–particles (1.79 MeV) and a desirable half–life of 14.3 days. With this half life we would expect to have a useful shelf–life of at least 2-4 weeks. Importantly, one–half of the total radiation dose is delivered in the first two weeks after the stent implantation, which is the time frame for maximum cellular proliferation after arterial injury. With this relatively short half–life there will be virtually no measurable radiation 4-5 months after the implantation (< 1/1,000th of initial activity).

The techniques for direct $^{32}$P ion implantation just beneath the surface of virtually any metal stent has been developed and is currently ready for manufacturing of commercial grade stents for clinical use. Finally, if deemed important, heparin or other antithrombogenic coatings can be applied to the stent after the $^{32}$P ion implantation procedure.

**Safety Issues Related to a Radioisotope Stent.**

There are a number of important features of a beta–particle emitting radioisotope stent that should make it safe for clinical use. First, as suggested above, the local nature of the radiation makes this approach quite safe. For the average lesion only 3-4 grams of vascular tissue will be irradiated. There is virtually no radiation administered beyond the adventitial layer. At the activity levels planned for the initial clinical trial (1 μCi for a 15 mm long stent) the amount of radiation delivered is very low. The total body radiation dose and total cardiac dose is estimated to be less that 1/1,000th of the fluoroscopy dose during an angioplasty. After ion implantation and careful washing of the stent there is minimal leeching of $^{32}$P from the stent surface (< 1% of total activity). The maximal amount of $^{32}$P that could leech off the stent is much less than the naturally occurring radiation in the human body.

In order to protect the operator from radiation the stent will come packaged with a 1.5 inch thick lucite plastic shield. This plastic shield effectively eliminates radiation exposure to the interventionalist. The stent will not be handled directly by the operator at any time. The end of the plastic shield is designed to be inserted into the opening of a standard Tuohy–Borst adaptor. The stent is then advanced directly into the guiding catheter and into the patient. The total radiation dose to the interventionalist implanting the stent is virtually immeasurable and much less than the dose from the scatter from the x–ray imaging source during an average PTCA procedure. When using beta–particle radiation sources such as this, there are no special shielding requirements in the cardiac catheterization laboratory.

Figure 1. Photomicrograph showing marked neointimal hyperplasia and luminal obstruction 7 months after stent implantation in the proximal left circumflex coronary artery of a cardiac transplant recipient.
**In vitro Results.** We have previously presented data from cell culture experiments examining the effects of external beam irradiation\(^{10}\) and local beta–particle irradiation from a stent wire\(^9\) to inhibit smooth muscle cell and endothelial cell proliferation. In Figure 2 the effects of a small amount of \(^{32}\)P imbedded beneath the surface of a titanium wire is shown in cell culture. After 10 days the smooth muscle cells (Figure 2A) (or endothelial cells, Figure 2B) were stained with toluidine blue. One can see a halo around the wire caused by the inhibition of smooth muscle cell growth within a 3-5 mm zone on either side of the wire (Figure 2A). In contrast, in Figure 2B, there is no evidence of inhibition of endothelial cell growth at the same wire activity (0.019 μCi/cm of wire) in the endothelial cell culture.\(^9\) Overall, there was approximately a 3–fold dose response shift observed in these studies, with proliferating vascular endothelial cells appearing much less sensitive to beta–particle irradiation than proliferating vascular smooth muscle cells.

**In vivo Studies.** Numerous animal studies and one human study have been reported demonstrating the ability of intravascular irradiation to inhibit neointimal hyperplasia following balloon angioplasty and/or stenting. We have previously

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**Figure 2.** Photomicrographs showing the effects of a \(\beta\)–particle emitting stent wire on vascular smooth muscle cell and bovine vascular endothelial cell growth at 12 days after plating. Cells were stained with toluidine blue and then photographed. In panel A there is evidence of no growth of smooth muscle cells within a range of 3-5 mm from the \(^{32}\)P impregnated stent wire (activity 0.019 μCi, magnification X 8). In B, endothelial cells can be seen growing over the stent wire at the same activity level as was used in A, (0.019 μCi, magnification X 50).
reported that external beam irradiation delivered five days after balloon injury significantly inhibits neointimal hyperplasia in a non diseased rabbit iliac model. Similarly, Sheffer et al. demonstrated that an externally applied single exposure of beta–particle irradiation profoundly inhibited neointimal hyperplasia following balloon injury in a rabbit ear artery model. Waksman and Weinberger have reported the ability of locally delivered arterial radiation (350-1400 cGy) from a high energy Iridium source to inhibit intimal hyperplasia in a porcine coronary artery, balloon injury model, with persistence of the favorable effect out to 6–months. Waksman’s group also noted improved efficacy in reducing neointimal hyperplasia when the radiation (700 cGy) was delivered two days following the balloon injury suggesting that the early and decaying delivery of radiation from a 32P stent may provide nearly optimal timing of radiation dosing to inhibit neointimal hyperplasia.

The efficacy of radioactive stents to inhibit neointimal hyperplasia has been demonstrated by Hehrlein, et al. in a non–atherosclerotic rabbit iliac model. This study showed marked inhibition of neointimal hyperplasia at 12 weeks following the implantation of radioactive stainless steel (Palmaz) half stent containing multiple radioisotopes (55,56,57Co, 52Mg, 55Fe). The favorable effects have now been observed to persist at one–year follow–up. Endothelial cell regrowth over these radioactive stents was demonstrated at 4 weeks after stent implantation. Laird and Carter, et al. have evaluated a 32P impregnated Strecker stent with a very low level of radioactivity (0.14 μCi) in a porcine iliac model. They demonstrated a 37% reduction in neointimal area in the radioactive stent segments versus the control stent (p=0.004, see Figure 3). They also demonstrated complete reendo–thelialization of the radioactive stented segments, and no histopathological evidence of medial injury at 28 days after stent implantation. Preliminary studies by Laird and Carter, et al. have also demonstrated a significant inhibition of neointimal proliferation at one month in a porcine coronary artery model using 32P Palmaz half–stents (7 mm length). The favorable effects were observed at stent activities as low as 0.15 μCi and at levels as high as 23 μCi. Overall, there was between 30% and 70% inhibition of neointimal area in the 32P stented segments compared to the control stents in this study. No aneurysm formation was observed in any of the radioisotope stents. Most recently Hehrlein et al. have also demonstrated the efficacy of beta–particle irradiation from a 32P impregnated Palmaz stent to inhibit neointimal hyperplasia in a rabbit iliac artery model of restenosis. Finally, a recently reported clinical experience with endovascular irradiation in the peripheral circulation has suggested that radiation may be very effective in preventing human arterial restenosis when combined with stenting.

**Ultra Low–Dose 32P Stents.** One of the more intriguing observations from the in vitro and recent in vivo testing of 32P stents is the ability of extraordinarily low activities (low radiation doses) to inhibit smooth muscle cell growth (in vitro) and neointimal hyperplasia (in vivo). The

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**Figure 3.** Cross-sectional photomicrograph of porcine iliac arteries 28 days after Strecker stent implantation. In panel A. (control stent) there is relatively concentric neointimal hyperplasia within the stented segment. In panel B. (32P impregnated stent, 0.014 μCi total activity) there is significant reduction in the neointimal response.
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observation that a 10 day dose of 20-30 cGy in vitro (cell culture) inhibited smooth muscle cell growth9 suggests that the beta–particle emission from a 32P source may inhibit migration of smooth muscle cells or have other nonspecific effects upon smooth muscle cell growth. The efficacy of a 0.14 μCi 32P stent in porcine iliac arteries and a 0.15 μCi 32P stent in porcine coronary arteries, also demonstrates that an ultra low dose 32P stent is capable of inhibiting neointimal hyperplasia in vivo.

In order to better understand the effects of ultra low activity stents we have performed computer–modeling of the near and far field radiation doses seen by the vessel wall at varying distances from the outer circumference of an expanded 32P Palmaz–Schatz stent. These computer–model–derived data have now been confirmed to correlate well with film dosimetry (unpublished data). These data demonstrate that a 0.5 μCi half stent would deliver approximately 200-300 cGy to the media during the first 14 days after stent implantation in a porcine coronary artery. This appears to be too low a dose to have an “afterloading” (cell kill) effect upon the media and adventitia. Importantly, as one moves closer to the stent wires, as a migrating smooth muscle cell would need to do to reach the luminal side of the stent, the migrating and dividing cell would encounter much higher radiation doses in this near field near the stent wires (up to 3,000 cGy/14 days). At this dose it is possible that a substantial subpopulation of the dividing smooth muscle cells could be disabled or killed as they attempt to migrate across this stent radiation “barrier.” We have referred to this intensification of the near field radiation dose and the associated barrier effect as the “electron fence” theory.

If this effect is confirmed it has several favorable implications for the safety and efficacy of beta–particle emitting radioisotope stents. One important implication of this “electron fence” theory would be that the geometry of the plaque and vessel wall after stenting would not likely influence the favorable effects since high levels of radiation to the media and adventitia would not be required to inhibit neointimal hyperplasia. In addition, since only low levels of radiation would be delivered to the media and adventitia this could prove to be a much safer method of delivering radiation as compared to any catheter–based approach in which between 1,000-3,000 cGy are typically delivered in a single brief dosing period to the deeper vessel wall structures. Finally, these very low doses also appear to allow rapid reendothelialization of the stent.16

Although there is increasing in vitro evidence to support this electron fence theory, it is also possible that the inhibition of neointimal hyperplasia at very low activities is related to an anti-migratory effect(s) or other poorly understood phenomena. Additional in vitro studies are planned to try to address the complex radiobiology of radioisotope stents.

Summary. Preliminary in vitro and in vivo studies suggest that local intra–arterial radiation delivered via a beta–particle emitting radioisotope stent may provide a safe and effective means to inhibit smooth muscle cell mediated neointimal growth after stent implantation. Complete dose–response testing, including longer–term follow–up studies in animal models are underway. Initial clinical evaluation of a 32P intracoronary stent started in October 1996. The ability of this approach to effectively reduce clinical restenosis after intracoronary stenting will ultimately require careful assessment in randomized clinical studies.

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