# Stents and biology combination for restenosis

Researchers, biotechnology companies, and physicians are beginning to combine both mechanical devices (stents) and drugs in preventing the reclosure of arteries (restenosis) following balloon angioplasty treatments for heart attacks. "While drugs sound better to many of us," says Jeffrey Leiden, chief of cardiology at the University of Chicago (IL) "stents seem to actually work better in dealing with the vascular cell proliferation that follows angioplasty, and we're not sure why." Recent results from clinical trials in Japan and Europe using stents from Johnson & Johnson (J&J, Warren, NJ) have certainly been too good for biotechnology to overlook (see "Stent Statistics").

As Leiden notes, restenosis is the result of the body's attempt to repair itself after the injury to the artery, which unavoidably accompanies ballon angioplasty. The molecular complexity of the "repair" process—which involves a great number of different growth factors, growth factor receptors, and cell cycle regulators—may account for the difficulty in designing a simple drug regimen. Stents—flexible cylinders implanted at the time of angioplasty that hold open the artery—seem to simplify the problem.

Centocor (Malvern, PA) plans to begin a trial in the next few weeks with ReoPro, its antiplatelet drug, and J&J's stent. ReoPro, a humanized monoclonal antibody directed against the 2β-3α growth complex, has already proved itself an effective treatment for restenosis. The drug was approved in the US in December 1994 for the reduction of acute cardiac ischemic complications in patients undergoing angioplasty at high risk for abrupt artery closure, and Centocor has been able to conclude trials in two other indications early because of positive results with the drug. "ReoPro . . . could, in the future, be used in conjunction with a thrombolytic as adjuncts to stents in angioplasty," says Lawrence Leung, chief of hematology and professor of medicine at Stanford University (Palo Alto, CA).

Biocompatibles' (Uxbridge, UK) phosphorylcholine (PC) has potential utility, not because of what it does, but because of what it does not do. PC is a phospholipid that makes up about 90% of the cell membrane's surface. When coated on stents and other cardiology products, it confers a certain inertness, minimizing fibrin adsorption, platelet adhesion and activation of the coagulation pathway that can lead to thrombus formations. The company believes that PC will, therefore, reduce the need for the antithrombotics now given with stent implantation.

Another combination technique is being developed by Isostent (San Carlos, CA), a new company with a β-emitting stent that forms a barrier through which cells can't migrate and proliferate. President and CEO Michael Kopp says such β–waves may also disrupt the DNA of rapidly dividing smooth muscle cells in the artery wall, yet do not affect other organs or surfaces. Isostent plans to enter the clinic with the stent in the first half of 1997. Isostent's device acts through radioactive emission, but it may nonetheless show the way for other approaches that use biological anticell-proliferation strategies.

*Vicki Brower*
*Additional reporting from Mima Predich*

## Stent statistics

The results of two studies using J&J's Palmaz-Schatz stent have recently been published. A three-year trial at the Kokura Memorial Hospital (Kitakyushu, Japan) with 143 patients (*New England Journal of Medicine*, 334:561-61) demonstrated that stents reduce restenosis: Only 2.1% of heart attack patients with stents required repeat angioplasty, whereas 7.7% of those without the devices did. Furthermore, after three years, the arterial internal diameter increased significantly, leading researchers to conclude that the stent did not delay restenosis, but prevented it.

A second trial (Circulation 93:412-422) conducted by researchers at Erasmus University (Rotterdam, The Netherlands), showed that heparin-coated stents eliminated subacute thrombosis, which often follows within the first 72 hours after implantation, and that they were 99% effective in keeping patients' diseased coronary vessels open during the first month after the procedure. Moreover, the heparin coating obviated the need to give patients anti-clotting medicine. *Vicki Brower*

## Early-stage restinosis therapeutics move ahead

Numerous other early-stage developments directed at atherosclerosis in general and restenosis in particular may eventually be used in combination with stents.

In March, Hyal Pharmaceuticals (Mississauga, Ontario, Canada) began a phase II Canadian trial with HYAL-BV5200 (hyaluronan, HA), a human extracellular matrix component to combat restenosis. HA is normally expressed in low amounts on endothelial cells, but is upregulated in inflamed (and malignant tissues), according to Hyal president and CEO Sam Asculai. This attracts cells like macrophages and monocytes bearing HA receptors, such as ICAM-1, CD44, RHAMM, CD38, VCAM, and other cell adhesion molecules. Administration of HA means that those receptors are occupied. Thus, HA "keeps things rolling," says Asculai. Preclinical studies support the notion that HA's effect on restenosis may be mediated, at least partially, by inhibiting the influx of cells to the site of arterial injury.

AtheroGenics (Norcross, GA) is also addressing the cell adhesion and inflammatory aspects of atherosclerosis and restenosis. Russell Medford, president and CEO, and R. Wayne Alexander, AtheroGenics' founders, are both professors of cardiology at Emory University (Atlanta, GA). They believe that atherogenic inflammation is a redox-sensitive process triggered by stress to the arterial walls (induced by factors such as smoking). The molecular targets for AtheroGenics' small molecule vascular protectants—AGI-HI and AGI-H15—are, therefore, such redox-sensitive transcription factors as NF-KB. In preclinical studies, the two agents suppress macrophage recruitment to the arterial wall. The company believes that they have potential utility in restenosis, as well as in inhibiting and reversing plaque deposits.

Preclinical studies with Gilead Sciences' (Foster City, CA) protein C activator (PCA) published in November 1995 (*Nature* 378:413-415) showed potent, dose-dependent anticoagulation without any increase in bleeding time. PCA is an engineered version of thrombin, but whereas thrombin has both coagulant and anticoagulant functions, PCA turns off procoagulant function, and does not promote fibrin clots, platelet

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