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Next-generation stents

By Steve Edelson, Executive Editor

Aachen University researchers have identified a neutrophil-derived protein called LL37 that provides an alternative to existing antiproliferative stent coatings geared mainly toward preventing restenosis.[1] The German team expects its coating, which induces endothelial recovery of the vasculature, could be combined with existing drug-eluting stent technology to reduce the incidence of late-onset thrombosis, which has cast a safety cloud over the devices.

When coated stents from **Johnson & Johnson** and **Boston Scientific Corp.** entered the market more than a decade ago, the products rapidly grabbed market share from bare metal stents. The rationale was clear: the products with antiproliferative coatings lowered the incidence of restenosis.

> **"First you would get endothelial healing promoted by LL37, and then you would block the new cells from growing out of control."**
> *—Christian Weber, Aachen University*

Over the years, however, the advantages of coated stents became less obvious as data showed they increased the risk of late stent thrombosis compared with the bare metal versions, possibly due to a lack of proper healing of the blood vessels following stent procedures.[2]

Indeed, J&J's Cordis Corp. unit announced plans in June to exit the coated stent market. Boston Scientific is the market leader for drug-eluting stents, but it reported flat sales of those products in the first nine months of the year compared with the same period in 2010 ($1.15 billion vs. $1.16 billion).

Although angioscopy and postmortem analyses have correlated late stent thrombosis to impaired endothelial recovery, the definitive mechanisms are unknown.

To tease out these mechanisms, the German team decided to focus on neutrophils—the first responders to the site of arterial injury. The group found a protective role for neutrophil-released granules that contained cathelicidin antimicrobial peptide (CAMP; LL37).

The protective role of LL37 was surprising because neutrophils are known to also release proinflammatory granules that can exacerbate multiple conditions including atherosclerosis.[3]

Next, the team engineered stents coated with LL37 and tested them in atherosclerotic mice. Animals receiving the coated stents had greater endothelial coverage and luminal area and less thrombosis than mice given stents lacking LL37.

Mechanistic studies revealed that LL37 triggers the release of two proangiogenic factors—VEGF and epidermal growth factor (EGF)—from early outgrowth cells. Those cells migrate to sites of injury and accelerate re-endothelialization.

Data were published in *Science Translational Medicine*.

Corresponding author Christian Weber, director of the Institute for Molecular Cardiovascular Research at Aachen University, described the model as "very stringent. Mice have a very tiny lumen—just like a human vessel that would likely be occluded within days. This was a very good model in which to test our coating."

Weber told *SciBX* a logical next step could be to engineer a stent coated with LL37 and an antiproliferative agent. "First you would get endothelial healing promoted by LL37, and then you would block the new cells from growing out of control," he said.

"Although our study was limited to four weeks after implantation, no thrombus formation was observed in these stents. Thus, stents exploiting proendothelial properties of LL37 may also be suitable to circumvent problems of late thrombosis in drug-eluting stents after longer periods of clinical use," the authors wrote in the paper.

"I've been working with LL37 in relation to glass coatings" to avoid microbial films, said Martin Malmsten, a professor of physical chemistry at **Uppsala University**. "It's remarkably nontoxic and quite multifunctional. A dual stent coating is a reasonable idea."

Malmsten also is a cofounder of **XImmune AB**, which is developing immune-modulating host defense peptides for infectious, inflammatory and pulmonary diseases.

Weber's team now plans to test the stent coating in larger animals. The paper's findings are unpatented and are available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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Boston Scientific Corp. (NYSE:BSX), Natick, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Uppsala University, Uppsala, Sweden
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