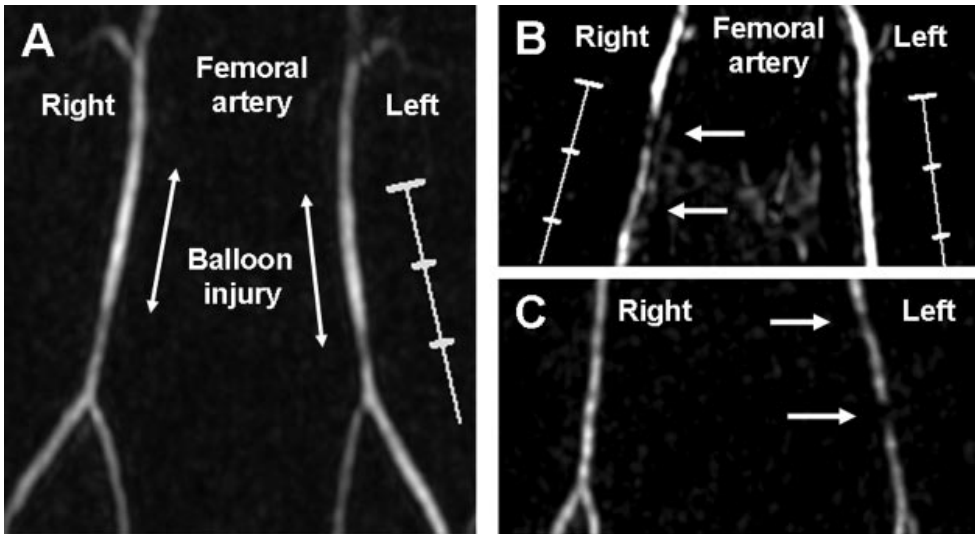
Nanoparticle-Mediated Inhibition of Restenosis

Patients with occluded or partially occluded coronary arteries are frequently treated with percutaneous angioplasty, where a balloon is used to open up the blocked vessel. It was discovered many years ago that the vessel tends to re-occlude due to proliferation of the cells in the vessel wall, and so where possible drug-eluting stents are used to prevent proliferation and keep the artery open. However, in some cases stents cannot be used due to anatomical complications. Drug eluting stents also suffer from the need for aggressive therapy to prevent the formation of blood clots. Alternate strategies to prevent restonosis of injured arteries would thus be useful.

Cyrus and colleagues have used local delivery of nanoparticles loaded with the anti-proliferative drug rapamycin to prevent restenosis in a rabbit model of vascular injury. The nanoparticles are composed of perfluorocarbon, and were targeted to $\alpha_v\beta_3$ integrins, proteins found on the outside of smooth muscle cells. These proteins are normally not accessible to the bloodstream, but are exposed by the damage to the vessel wall caused by inflating a balloon in the femoral arteries of the rabbits.



Immediately after balloon injury, nanoparticle (left) and saline treated (right) femoral arteries have normal blood flow (A). Two weeks later, arteries treated with drug-containing targeted nanoparticles remain open(B, left, C right). Arteries treated with nanoparticles without drug (B, right) or with drug but without targeting agent (C, left) show partial occlusion due to proliferation of the vessel

The figure shows that when the femoral arteries of a rabbit were damaged by overinflating a balloon, blood flow was normal 40 minutes later whether the artery was treated with saline or with targeted drug-containing nanoparticles. However, two weeks later, arteries treated with the targeted rapamycin-containing nanoparticles remained completely open, while omission of drug or targeting agent from the nanoparticles resulted in partial occlusion of the artery. Histological studies confirmed that proliferation of the vessel wall occurred due to the injury but was blocked in the arteries treated with the targeted rapamycin-containing nanoparticles. Importantly, the drug treatment did not delay endothelial healing; impaired healing would be detrimental due to increased risk of blood clots. This promising technology could potentially be used during clinical interventional procedures to prevent restenosis in patients.

Cyrus T, Zhang H, Allen JS, Williams TA, Hu G, Caruthers SD, Wickline SA, Lanza GM: Intramural delivery of rapamycin with $\alpha_v\beta_3$ –targeted paramagnetic nanoparticles inhibits restenosis after balloon injury. *Arteriosclerosis, Thrombosis and Vascular Biology* 2008:820-826, May 2008.

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