avoiding the need for toxic chemicals, such as solvents, in the administration process, thus potentially improving safety through the elimination of solvent-related side effects.

[0005] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

~~BRIEF~~ SUMMARY ~~OF THE INVENTION~~

[0006] The present application in some embodiment provides a method of delivering a composition comprising nanoparticles comprising albumin and a macrolide to a blood vessel, wherein the method comprises injecting into the blood vessel wall or tissue surrounding the blood vessel wall an effective amount of a composition comprising nanoparticles comprising a macrolide and an albumin.

[0006a] In one aspect, there is provided the use of a composition comprising nanoparticles comprising rapamycin or a derivative thereof and an albumin in the manufacture of a medicament for treating restenosis in a blood vessel in an individual in need thereof, wherein the medicament is to be injected into the blood vessel wall or tissue surrounding the blood vessel wall, and wherein the treatment is characterized by inhibition of negative remodeling and/or vascular fibrosis in the blood vessel.

[0006b] In some embodiments, there is provided a method of inhibiting negative remodeling in a blood vessel in an individual in need thereof, comprising injecting into the blood vessel wall or tissue surrounding the blood vessel wall an effective amount of a composition comprising nanoparticles comprising a macrolide and an albumin. In some embodiments, there is provided a method of inhibiting vascular fibrosis (such as medial fibrosis or adventitia fibrosis) in a blood vessel in an individual in need thereof, comprising injecting into the blood vessel wall or tissue surrounding the blood vessel wall an effective amount of a composition comprising nanoparticles comprising a macrolide and an albumin. In some embodiments, there is provided a method of reducing proliferation index in a blood vessel in an individual in need thereof, comprising injecting into the blood vessel wall or tissue surrounding the blood vessel wall an effective amount of a composition comprising nanoparticles comprising a macrolide and an albumin. In some embodiments, there is provided a method of promoting positive remodeling in a blood vessel in an individual in need thereof, comprising injecting into the blood vessel wall or tissue surrounding the blood vessel wall an effective amount of a composition comprising nanoparticles comprising a macrolide and an albumin.

[0007] In some embodiments, the blood vessel is an artery, such as a coronary artery or a peripheral artery. In some embodiments, the artery is selected from the group consisting of renal artery, cerebral artery, pulmonary artery, and artery in the leg. In some embodiments, the blood vessel is a vein.

[0008] In some embodiments, the nanoparticle composition is injected into the blood vessel wall. In some embodiments, the nanoparticle composition is injected into the tissue surrounding the blood vessel wall. In some embodiments, the nanoparticle composition is injected into the adventitial tissue of the blood vessel.

[0009] In some embodiments, the nanoparticle composition is injected at a dose of about 0.001 mg to about 100 mg, including for example about 0.05 mg to about 5 mg. In some

embodiments, the injection volume of the nanoparticle composition is about 0.01ml to about 50 ml, including for example, about 0.5 ml to about 5 ml. In some embodiments, the nanoparticle composition is injected though a catheter with a needle, such as a deployable needle. In some embodiments, the nanoparticle composition is injected at least once a year. In some embodiments, the nanoparticle composition is injected only once.

[0010] In some embodiments, the nanoparticle composition is injected distal to the disease site. In some embodiments, the nanoparticle composition is injected proximal to the disease site. In some embodiments, the nanoparticle composition is injected at or adjacent to the disease site. In some embodiments, the nanoparticle composition is injected remotely from the disease site. In some embodiments, the nanoparticle composition is injected at least about 2 cm (including for example at least any of 3, 4, 5, 6, 7, 8, 9, or 10 cm) away from the disease site.

[0011] In some embodiment according to any of the above embodiments, the individual has any one of: angina, myocardial infarction, congestive heart failure, cardiac arrhythmia, peripheral artery disease, claudication, or chronic limb ischemia. In some embodiments, the individual is a human. In some embodiments, the method is carried out during vascular interventional procedure, including but not limited to, angioplasty (such as percutaneous translumenal coronary angioplasty), stenting, or atherectomy. In some embodiments, the method is carried out after a vascular interventional procedure, including but not limited to, angioplasty, stenting, or atherectomy.

[0012] In some embodiments according to any of the above embodiments, the macrolide is rapamycin or a derivative thereof. In some embodiments, the macrolide is rapamycin. In some embodiments according to any of the above embodiments, the nanoparticles in the composition have an average diameter of no greater than about 200 nm, such as no greater than about 100 nm. In some embodiments, the nanoparticles in the composition have an average diameter of no less than about 70 nm. In some embodiments, the macrolide in the nanoparticles is coated with albumin.

[0013] Also provided are kits and devices for use in any of the methods described herein. For example, in some embodiments, there is provided a catheter with a needle (such as a deployable needle), wherein the needle contains a composition comprising nanoparticles comprising a macrolide and an albumin. In some embodiments, the macrolide is rapamycin.

[0013a] In one aspect, there is provided a catheter with a needle, wherein the needle contains a composition comprising nanoparticles comprising rapamycin or a derivative thereof and an albumin.

[0013b] In some embodiments, the nanoparticles comprise a macrolide coated with albumin. In some embodiments, the nanoparticles in the composition have an average diameter of no greater than about 200 nm, such as no greater than about 100 nm. In some embodiments, the nanoparticles in the composition have an average diameter of no less than about 70 nm.

[0014] These and other aspects and advantages of the present ~~invention~~disclosure will become apparent from the subsequent detailed description and the appended claims. It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present ~~invention~~disclosure.

BRIEF DESCRIPTION OF FIGURES

[0015] Figure 1 provides images of the micro-infusion catheter utilized for periadventitial injection of *Nab*-rapamycin in the femoral artery. Figure 1A shows a deflated balloon which sheathes the needle. Figure 1B shows an inflated balloon with the needle extruding outward.

[0016] Figure 2 provides two flow charts for the study design involving periadventitial injection of *Nab*-rapamycin in a porcine femoral artery balloon angioplasty injury model. Figure 2A shows a flow chart for pharmacokinetics studies. Figure 2B shows a flow chart for histopathology studies.

[0017] Figures 3A-F show a representative angiogram series for periadventitial injection of *Nab*-rapamycin in the femoral artery.

[0018] Figures 4A-4D show reduction of luminal stenosis after periadventitial delivery of *Nab*-rapamycin as measured by mean lumen cross-sectional area (4A), mean artery cross sectional area (4B), mean percent luminal stenosis (4C), and average medial fibrosis (4D).

[0019] Figures 5A and 5B show the pharmacokinetics of *Nab*-rapamycin after periadventitial delivery in femoral arteries as measured by serum rapamycin concentration (5A) and tissue rapamycin concentration (5B).

[0020] Figures 6A-6D show histopathology staining of femoral arteries treated with (6C and 6D) or with (6A and 6B) *Nab*-rapamycin by periadventitial delivery. Figures 6A and 6C show staining with H&E. Figures 6B and 6D show staining with trichrome.

[0021] Figure 7A shows the proliferative index after periadventitial delivery of *Nab*-rapamycin or a control. Figure 7B shows the endothelialization after periadventitial delivery of *Nab*-rapamycin or a control.

[0022] Figure 8A shows the proliferative index after periadventitial delivery of *Nab*-rapamycin at days 3, 8, and 28. Figure 8B shows the endothelialization after periadventitial delivery of *Nab*-rapamycin at days 3, 8, and 28.

[0023] Figure 9A shows adventitial leukocyte infiltration after periadventitial delivery of *Nab*-rapamycin or a control at days 3, 8, and 28. Figure 9B shows mean number of adventitial vessels after periadventitial delivery of *Nab*-rapamycin or a control at day 28.