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“Venopathy” at Work: Recasting Neointimal Hyperplasia in a New Light

Alexander S. Yevzlin, Micah R. Chan, Yolanda T. Becker, Prabir Roy-Chaudhury, Timmy Lee, and Bryan N. Becker

Departments of Medicine and Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, and Department of Medicine, University of Cincinnati, Cincinnati, OH

Abstract

Hemodialysis vascular access is a unique form of vascular anastomosis. Though created in a unique disease state, it has much to offer in terms of insights into venous endothelial and anastomotic biology. The development of neointimal hyperplasia has been identified as a pathologic entity, decreasing the lifespan and effectiveness of hemodialysis vascular access. Subtle hints and new data suggest a contrary idea—that neointimal hyperplasia, to some extent an expected response, if controlled properly, may play a beneficial role in the promotion of maturation to a functional access. This review attempts to recast our understanding of neointimal hyperplasia and redefine research goals for an evolving discipline that focuses on a life-sustaining connection between an artery and vein.

Keywords

hemodialysis vascular access; venous endothelium; neointimal hyperplasia; arteriovenous fistula; arteriovenous graft

Introduction

One cannot avoid the realization that hemodialysis vascular access is a unique form of vascular anastomosis. Moreover, it is created in a discrete disease state subject to periodic fluctuations in blood volume, a relative constancy of inflammation and aberrant regulation of acid-base and electrolyte states. Changes in these parameters could incite stimuli that trigger aspects of neointimal hyperplasia (NH), the pathologic *sine quo non* of access dysfunction. Added to those chronic physiological stimuli are the serial changes in blood volume, hydrostatic pressure, shear stress and repeated vessel trauma that accompany a dialysis procedure.

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To whom correspondence should be addressed: Bryan N. Becker, MD, MMM, FACP J5/223 CSC 600 Highland Avenue Madison, WI 53792.

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Hemodialysis access dysfunction remains a \$1 billion per year problem (1) despite recent efforts by Centers for Medicare and Medicaid Services (CMS), the End-stage renal disease (ESRD) networks, and other national institutions to improve outcomes. Two recent, multicenter, NIH-sponsored clinical trials (2, 3) designed to provide definitive solutions to the problem of arteriovenous fistulae (AVF) failure to mature have been largely unsuccessful and, at best, have raised more complex questions. Given the growth of the US hemodialysis population pegged at 774,000 patients by 2020 (1) and the limited success of recent clinical investigations to clearly define a solution, an urgent need exists to begin a comprehensive translational research initiative involving endothelial biologists, nephrologists, surgeons, and interventionalists to elucidate mechanisms and more effective therapies for NH and vascular stenosis.

NH has been characterized as the primary pathologic lesion in hemodialysis access grafts and fistulas that develop stenosis (4, 5) (Figure 1). There is also evidence, though limited, that implicates NH in fistula nonmaturation (6). While NH has been regarded as a pure pathologic entity with substantial research efforts directed at preventing and treating NH in vascular access (7, 8) we would suggest that NH, to some extent, may be a prerequisite for the evolution of a functional dialysis vascular access. Recent contributions have cast “venopathy” in general, and NH, in particular, in a new light (Figure 2):

1. Vascular remodeling is a balance between NH and vascular dilation following creation of the AV anastomosis. NH and medial hypertrophy may be salutary in a maturing access when occurring in association with positive (outward) vascular remodeling (dilation).
2. NH has been observed in native veins prior to access placement suggesting that abnormal shear stress after arteriovenous access creation is not the sole factor influencing the development of NH.

These hypotheses are important ultimately in driving clinical care. Fistula use is much higher among hemodialysis patients in Europe and Japan, compared to the United States (9, 10). Moreover, the Japanese experience differs from that of the US in that over 70% of Japanese AVFs are cannulated within the first two weeks of placement, compared to less than 5% in the US (9). A more refined understanding of NH and our ability to control it could narrow the gap in maturation rates, early AVF use, and decrease catheter bridging in the US hemodialysis population.

This review recasts our understanding of NH and sets research goals for an evolving discipline that focuses on a life-sustaining connection between an artery and vein. Our perspective on NH must evolve towards understanding NH as a critical therapeutic target.

The traditional view of NH

Shear stress and hemodynamic changes in NH—To understand potential regulation of this process, it is necessary to examine mechanisms traditionally implicated in the genesis of NH in hemodialysis vascular access, including proliferation and migration of smooth muscle cells (SMC) from the media, aggravation of inflammation, alteration of hemodynamic forces, and activation of the coagulation cascade (11)

The initial understanding of NH pathology derived from studies of coronary or peripheral arterial disease. This work suggested vascular SMC in media proliferate and migrate into intima. However, adventitial remodeling was also noted in coronary arteries. NH in the arterial circulation (as in peripheral arterial grafts) however can be dissimilar to NH in the venous circulation (as in a dialysis fistula, Figure 3) (5).

Non-laminar blood flow, oscillatory shear stress, and increased turbulence following creation of an AV anastomosis result in aggressive NH; and patency of the venous conduits is generally worse than the patency of bypass grafts in the arterial circulation. In an arteriovenous graft (AVG), the presence of a foreign body adds bioincompatibility that augments local inflammation compounded by repeat injury from dialysis needles and uremia-associated endothelial dysfunction. Changing rheology and increased blood flow induce regression of NH in polytetrafluoroethylene (PTFE) grafts (12). Whether this is also true for AVF however has not been determined.

NH has been studied in humans and in animal models. In one study, human venous tissue obtained from three patent and one thrombosed AVF was examined. NH was present together with medial hypertrophy resulting in greater than 80% stenosis with a predominance of myofibroblasts (6).

Analysis of NH in dialysis AVG revealed SMC and myofibroblast proliferation at the venous anastomosis and downstream vein (5). Angiogenesis was prominent in the adventitia and neointima. In addition, there was increased growth factor expression from SMC, myofibroblasts, microvessels, and macrophages. In other models, cytokines related to oxidative stress have been expressed (13)(14).

Interestingly, after primary stenoses have been treated with angioplasty in AVFs, there is a significant increase in the proliferative index in medial and intimal lesions (4). This suggests that angioplasty-induced vascular injury enhances growth factor and cytokine expression. Thus, paradoxically, the procedure to treat venous stenoses may be responsible for aggressive dialysis access stenosis.

On the basis of the pathogenesis of NH, a mathematic model of venous NH has been developed (15). The model anticipates possible access stenosis and indications for intervention. What is more difficult to track but also significant is that venous endothelium *per se* may be able to promote NH (16).

Genetics, inflammation and NH—Genetic factors have been linked to the development of aggressive NH. Single nucleotide polymorphisms (SNPs) in matrix metalloproteinase (MMP) and angiotensin converting enzyme genes can alter vascular responsiveness. The latter has been investigated in the context of hemodialysis access patency. Polymorphisms of TGF- β , heme oxygenase 1 (HO-1), and the methylene tetrahydrofolate reductase gene also have been linked to AVF patency (17-20).

Among these polymorphisms, HO-1 has the greatest likelihood of a direct association with access outcomes. HO-1 is an inducible protein, regulating vascular response to injury, decreasing NH and inflammation. HO-1 deficiency is linked with NH and inflammation. In

experimental AVF creation, HO-1 null mice have increased MMP expression and an increased number of occluded AVF compared to wild-type (21).

Far-infrared therapy also increases blood flow and patency of AVF in HD via HO-1 presumably through thermoreceptor activation and concomitant reduction in endothelial inflammation (22). HO-1 is likely the mechanism too for the salutary effects of rapamycin and paclitaxel in decreasing AVF stenosis. Thus, delivery of HO-1 into the AV anastomosis could theoretically prevent NH or even induce regression of NH.

Inflammation has to be considered an auxiliary if not primary stimulus for NH in dialysis access. Levels of inflammatory biomarkers in surgically harvested thrombosed fistulae are elevated (23). This finding has been corroborated by evidence of inflammation around NH lesions, including increased expression of IL-6 and vascular cellular adhesion molecule-1 (VCAM-1).

Lee et al. recently documented venous NH prior to AVF or AVG creation in venous segments at the site of AV access creation (TL, personal communication). The stimuli driving this venous NH are unknown. Theoretically, subtle degrees of increased sheer stress induced by increased intravascular volume could be a stimulus. Additionally, the inflammatory milieu of kidney failure could be a stimulus for this de novo NH. It is as yet unclear as to whether pre-existing NH correlates with patency or a reduction in patency in subsequent AVF creation.

Regulating NH: Current and Future Treatment Modalities

The approach to NH in dialysis access so far has been clinically mechanistic, consisting of repeat interventions with angioplasties and stent placement. These therapies might be successful in the short term in altering NH. However, long-term patency remains elusive. The ability to *regulate* NH, not just eradicate or prevent it for any potential benefit is unknown. Inward remodeling (what is currently called “NH”) and outward remodeling (what is currently called “vascular maturation”), rather than distinct pathologic processes, can be viewed as two polar aspects of vascular remodeling. Broader-based investigations are needed to elucidate this potentially misunderstood relationship between “good” and “bad” remodeling and refocus therapeutic efforts from “suppression” to “control” (Table 1, Figure 4).

Pharmacologic interventions—The effect of short-term local pharmacologic interventions on NH in AV grafts has been evaluated in different animal models. A beneficial effect in an animal model, however, does not necessarily translate into a clinical benefit in dialysis patients given differences in vascular properties, responsiveness to drugs among species, effects of uremia, the short-term nature of these studies, and the use of surrogate outcomes. While a perivascular paclitaxel wrap inhibited graft stenosis in a pig model (24), a clinical trial evaluating a paclitaxel wrap on graft failure was suspended pending a safety review. A pilot study demonstrated the safety of a sirolimus-eluting collagen matrix implanted during graft surgery (25). Alternatively, edifoligide, an E2F transcription factor decoy, did not prevent coronary or peripheral bypass graft failure (26). Other experimental approaches being evaluated include most significantly, the development

of autologous tissue-engineered vascular grafts (27). One obvious strategy to consider is the application of these interventions shortly after creation of the AVG to potentially allow processes to initiate NH that can be subsequently regulated.

A number of vasoactive drugs have the potential to alter NH in dialysis vascular access. These agents include platelet antagonists, calcium channel blockers, angiotensin-converting enzyme inhibitors, and fish oil. Other agents that can affect vascular remodeling include statins, peroxisome proliferator-activated receptor agonists, and immunosuppressive agents. Imatinib mesylate, a phosphotyrosine kinase inhibitor of PDGF, as well as Bcr-Abl and C-kit, are also possible therapeutic agent or targets. While delivery of these agents at the time of surgery could be straightforward, repeat delivery, particularly for agents with a short half-life could be challenging. Initial work using endovascular balloons with sheathed needles to pierce the vessel wall demonstrate feasibility (28).

There has also been interest in exploring nonpharmacologic approaches to affect NH including radiation therapy. Ionizing radiation can induce apoptosis and inhibit the cell cycle. SMC in their proliferative phase in neointimal tissue are likely to be especially susceptible. In tissue culture, external beam radiation to SMC inhibited growth in a dose-dependent manner. Venous SMC were less susceptible than aortic SMC (29). Endovascular radiation therapy also inhibited NH *in vitro*, in porcine models of AVG, in human coronary artery stenosis, and in saphenous vein graft stenosis (30). In one study of local radiation therapy at the venous anastomotic site delayed site-specific graft stenosis though it did not improve cumulative graft survival (31). Another prospective, randomized, controlled study of one year of far-infrared therapy improved access flow and patency in patients who received the therapy (22). The Beta Radiation for Treatment of Arterial-Venous Graft Outflow (BRAVO) 1 study, randomly assigned 25 patients with dysfunctional AVG to brachytherapy or sham treatment after angioplasty (31). Primary patency at 6 months was 42% in the intervention group and 0% in the control group. Interestingly, secondary patency at 6 or 12 months was not affected. Thus, in aggregate, there are probably benefits to radiation therapy reducing AVG stenosis rates with a potential benefit on primary AVG patency. Other non-pharmacologic treatments could include local application of physical agents such as photodynamic or ultrasonic therapy *via* intravascular or external application as well as percutaneous balloon cryoplasty. The last has shown promising results (32).

Cellular and gene therapies—It is possible to deliver cells that promote healthy remodeling at sites of NH. Endothelial cells embedded in absorbable gelatin have been used to wrap around arteriovenous anastomoses to augment cytokine production and control NH in porcine AVF models. *In vivo* seeding with anti-CD34 antibodies accelerates endothelialization of new AVGs in a porcine model (33). Paradoxically, this therapy resulted in an increase in venous NH at the graft-vein anastomosis, again suggesting that regulating NH is critical and not an all-or-none process in AVG.

Gene transfer of endothelial and inducible nitric oxide synthase, cyclin-dependent kinase inhibitors, retinoblastoma protein, hepatocyte growth factor, and transcription factors such as edifoligide have all been used to inhibit NH in experimental angioplasty models (29). Gene therapies have focused on other targets as well such as adenoviral-mediated delivery

of β -adrenergic receptor kinase (β ARK), leading to a reduction in NH at the venous anastomosis through disrupted Gi signaling (30). Adenoviral transfer of C-type natriuretic peptide also improved outward remodeling and thickening of venous media in a porcine AVG (31), while perivascular placement of adenoviral vector containing vascular endothelial growth factor D is currently in phase III clinical trials for the prevention of AVG venous anastomotic stenosis (32). All of these treatments however have a) the risks of the vector *per se*; b) the unpredictability of distribution of vector and target molecule; and c) a patency-related outcome that while important still leaves open the questions as to the actual events within the dialysis access that might affect the outcome.

IV. Research Opportunities

Fundamentally, how do we bring together the unique and interesting observations regarding NH into a synthetic thesis that begets additional and novel ideas regarding therapy and prevention? Traditionally, NH associated with hemodialysis vascular access has been viewed as a vascular SMC lesion. However, with a greater understanding of cellular responses, it is apparent that other events are also occurring. There are studies that have described increased expression of TGF- β 1, latent TGF- β 1 binding protein-1 and TGF- β 1 mRNA in stenotic AVF (23). Ikegaya et al. (34) described elevated erythropoietin receptor and TGF- β 1 expression in stenotic AVF in patients who underwent chronic hemodialysis.

TGF- β 1 increases plasminogen activator inhibitor-1 (PAI-1) expression. Thus, it is not surprising that PAI-1 expression is increased in stenotic AVF (35). Interestingly, Lazo-Langner et al. (19) demonstrated in a cohort analysis that the risk of dialysis access thrombosis was differentially associated with polymorphisms in the TGF- β 1 gene that correlated with TGF- β 1 production. This risk was further modified through an interaction with the PAI-1 genotype present (19).

Traditional therapies that might antagonize TGF- β 1, e.g. ACE-inhibition, appear to have little effect reducing NH or maintaining access patency. However, type I and II TGF- β 1 receptor inhibition has yet to be examined as a potential therapy for hemodialysis access NH. Bone morphogenic protein-7 (BMP-7) might also be a therapy to affect this lesion. Choi and colleagues recently described an AVF model in mice in which BMP-7 administration reduced NH (36). Non-traditional sources of TGF- β might also be associated with AVF NH. Jin et al. (37) induced AVF in dogs and noted that chymase- and TGF- β (+) mast cells were prominent in proliferating neointima and media. Chymase inhibition reduced neointimal formation.

Is endothelial-mesenchymal transition a mechanism driving hemodialysis access NH?—With a solid body of literature suggesting at least a role for TGF- β 1 in hemodialysis access NH, it makes sense to consider how venous endothelium contribute to the process. Endothelial cells undergo mesenchymal transition in certain settings (38-41). The characteristic transformation to myofibroblasts is defined by the loss of cell surface adhesion and de novo expression of vimentin with a resulting decline in CD31 expression. The presence of myofibroblasts in lesions of NH could be a manifestation of not just SMC's in transition but also endothelial-mesenchymal transition (End-MT).

This is no doubt exploratory; yet, it is striking to note that intimal thickening involves transdifferentiation of embryonic endothelial cells (42). Moreover, CD40 and CD40 ligand (CD40L) have been identified at sites where endothelial cells differentiate into mesenchymal cells. CD40L is manifest with platelet activation and repeated injury to an access via needlesticks is an obvious theoretical stimulus for excess CD40L. It would be fascinating to ascertain CD40 and CD40L in a dialysis access at various stages of NH formation, or even immediately following access placement and then after repeated needle placements.

Other markers of potential End-MT could also be assessed in access tissue including NF- κ B activated p50/p65 heterodimers, I κ B, insulin-like growth factor-II (IGF-II), vitronectin, and whether S100A4 is expressed in cells obtained from human AVFs. A constellation of such findings would suggest that End-MT is present and possibly contributing to myofibroblast presence in NH.

Elastase, small GTP-binding proteins, and immunosuppressive medications—

A key feature of NH in vascular access is disruption of the internal elastic lamina (IEL). Chang and colleagues used gene expression analysis to study the impact of flow velocity and pressure on IEL in an aorto-caval fistula model (43). They noted an increase in cathepsin K and S, MMP2 mRNA, and elastase levels. Immunohistochemical studies localized cathepsin to the venous luminal endothelium lining the IEL.

These findings lay groundwork for studies that could examine local application of recombinant human elastase to promote vasodilation after fistula creation (44). Additional elastases may be necessary to regulate NH. Alternatively, different agents could be tried as therapeutics to regulate NH. The novel immunosuppressive agent, FK778, exerts an anti-proliferative effect on multiple cell types, limiting NH in vein graft models (45, 46).

Similarly, signaling cascades not traditionally targeted in dialysis access NH merit attention. Inhibition of Rho kinase suppresses neointimal formation in models of vascular injury (47-50) and alters endothelial cell migration (51). However, the identification of specific Rho kinase isoforms, e.g. ROCK1 or 2, in venous endothelial cells and the effects of Rho kinase *in vivo* are unknown. ROCK inhibitors are being evaluated as potential therapeutic agents for a number of vascular processes (52) and there is no reason to exclude them from studies addressing vascular access stenosis.

Delivery mechanisms—The systemic effects of agents targeting cathepsin K and S (53, 54), have stimulated study of delivery mechanisms. Vectorially directed scaffolds and nanoparticles with periodic, concentrated molecule delivery require more in-depth investigation. Lim and colleagues improved control of drug release through paclitaxel (Ptx)-loaded poly(lactico-glycolic acid) (PLGA) nanoparticles (55). The Ptx-PLGA-NPs were prepared and transferred to the luminal surface and inner part of ePTFE vascular grafts through a micro-tube pumping, spin penetration process. This system achieved controlled drug delivery. The science of molecular packaging, molecular measurement in the microenvironment, molecular sequestration in the microenvironment to reduce systemic side effects, and ultimately, the effect on true clinical outcome are all areas of needed emphasis and inquiry.

Imaging—With NH, we can measure systemic parameters or treatment parameters but the event is happening in a vessel anastomotic area over a period of time. New imaging methodologies such as surface dissolution imaging and atomic force microscopic topography could be used for intra-vital microscopy to assess changes in animal models of venous NH. Other non-destructive, non-linear optical microscopy techniques using harmonic generation and fluorescence (51) are options for experimental analyses. Intravascular ultrasound (IVUS) has been used in coronary and peripheral intervention to gauge successful therapy experimentally and clinically (Figure 5).

Physical measures—Ex-vivo models of hemodialysis suggest that high blood flow (500 ml/min) can shear off endothelial cells and reduce nitric oxide formation (56). It would be interesting to determine if different techniques, e.g. buttonhole cannulation, lead to less trauma and changes in activation of various molecular mediators and genes. Alternatively, are there differential patient responses to NH based on site of access creation and consequent flow? Are there non-traditional receptor subtypes, e.g. cannabinoid receptors, (57, 58) activated in the presence of needle jet turbulence or shear stress? These questions are answerable and could lead to better patient predictors of access patency over time.

Translational science and hemodialysis vascular access—Dialysis vascular access dysfunction is a unique form of venous pathology with a frequent of complications that yields an opportunity for mechanistic and translational studies focusing on the vascular injury that drives NH. Numerous studies have honed in on SMCs and their migratory predilection for a neointimal hyperplastic lesion, extrapolating mechanisms from other studies involving AVG and NH. The venous side of the AVF seems overtly susceptible to injury and serves as a nidus for the NH lesion that ultimately limits access patency. Our understanding of the interaction of inflammatory, cellular, genetic, and hemodynamic mechanisms at play in NH however has been limited by the conviction that NH is pathologic *per se*. In truth, NH may simply be a controllable response to a variety of stimuli. Clinical programs designed to provide comprehensive access care are in a unique position to more rigorously define the science of venous endothelial transformation. Cells could be initially harvested from the peri-anastomotic region at time of access creation for study and compared to cells harvested at time of endovascular intervention (59). The biology of this venopathy, whether it relates solely to the venous arm of the dialysis access or to more fundamental mechanisms of venous endothelial biology has the potential to help develop new technologies, new mechanisms of cell monitoring and novel vascular therapies. Dialysis AVF and AVG could be the ideal clinical model for testing novel local therapies for neointimal hyperplasia because of their superficial location, distance from major anatomical structures, easy repeated access to patients and their grafts and fistulas, and aggressive clinical course of neointimal hyperplasia.

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Figure 1. Neointimal hyperplastic lesions of various degrees in a porcine model of AVF. A: Mild NH; B: Moderate NH; C: Severe NH with luminal compromise

Figure 2.

Neointimal hyperplasia of vascular access can develop and progress through several pathways. A: Normal vein prior to access creation; B: No vascular remodeling after access creation; C: Luminal narrowing (NH) resulting in luminal compromise due to smooth muscle proliferation and inflammation; D: outward dilatation (maturation) resulting in luminal preservation of the AVF.

Figure 3. Neointimal hyperplasia in the lumen of an AVG (A), in the lumen of a stent (B), and in native vein (C) are traditionally regarded as the same pathologic process, but little is currently known about the genetic, cellular, and inflammatory differences in the three types of lesions.

Figure 4.

Broad translational investigative efforts can begin to unravel the complex interplay of NH and its pathologic origins and therapeutic targets (arrows can be understood as “processes leading to understanding of other processes” in this diagram. Note: arrows may become bidirectional as our understanding of NH develops).

Figure 5. IVUS imaging of AVF lesions. Mild (A), moderate (B), and severe (C) NH lesions. White circle – lumen of AVF. Black arrow – NH. Dark circle – ultrasound transducer. Note that ultrasound transducer occludes the lumen of the AVF in the severe lesion (C).

Table 1

Molecular targets of potential intervention in NH

Table 1. Therapeutic Targets in Neointimal Hyperplasia.		
Molecular Target	Mechanism of Action	Therapeutic Potential
TGF β 1	TGF β ₁ receptor complex signals through an intracellular serine/threonine kinase domain on the type I receptor and phosphorylates downstream substrates, such as Smad proteins. This induces transcription factors involved in angiogenesis as well as expression of endothelial growth factor, leading to cell proliferation and migration.	Direct antagonism of type I and II receptors
HO-1	HO-1 catalyzes the rate-limiting step in the degradation of heme, resulting in the liberation of iron, carbon monoxide (CO), and biliverdin. In vascular smooth muscle cells, CO exerts its antiproliferative effects via the p38 and MAPK pathway.	Inducible HO-1 via mTOR inhibitors
MTHFR polymorphism	MTHFR regulates homocysteine (Hcy) levels by remethylation to methionine. Hcy via production of reactive oxygen species can be toxic to the endothelium; it enhances vascular smooth muscle cell proliferation, increases platelet aggregation and thromboxane and antagonizes NO. _	Pharmacogenetic therapy against SNPs, thermoregulatory effects
IL-6	IL-6 is a pleiotropic cytokine that binds to a specific IL-6R (a chain, IL-6R, or CD126) on target cells. IL-6 is implicated in proliferation pathways by actions on growth factors, such as heparin-binding epithelial growth factor and hepatocyte growth factor.	Anti-IL-6 mAb
VCAM-1	VCAM-1 protein is an endothelial ligand for α 4 β 1 of the β 1 subfamily of integrins, and for integrin α 4 β 7. Its expression promotes the adhesion of lymphocytes, monocytes, eosinophils, and basophils.	VCAM-1 mAb, PPAR-activating drugs, proteosome and cell adhesion inhibitors
BMP-7	BMP-7 exhibits anti-inflammatory activity by downregulating intercellular adhesion molecule-1 (ICAM-1) expression and prevents transdifferentiation of smooth muscle cells into osteoblast-like cells in the vessel wall in the context of uremia and atherosclerosis.	Sequential delivery via PLGA nanoparticles loaded with BMP-7
Chymase	Serine protease that cleaves angiotensin I at same site as ACE and locally converts angiotensin I to angiotensin II inducing TGF- β and type III collagen formation. Chymase expression strongly upregulated in smooth muscle cells and stored in mast cells.	Novel chymase inhibitors
MMP 2	Zn ⁺² dependent endopeptidase, synthesized and secreted in zymogen form. Primary function is the degradation of proteins in the extracellular matrix and smooth muscle cell proliferation. Regulated through TIMP-2 and its cell surface receptor, MT1-MMP.	PI3K and MMP 2 inhibitors