Methods: Type 1 diabetes was induced to apolipoprotein E deficient mice (male, 8-week old) by streptozotocin injection. Diabetic animals were treated with either the HSP90 inhibitor 17-(dimethylaminoethylamino)-17-demetoxygeldanamycin (DMAG, 2-4 mg/kg body weight/day, i.p., every second day, 10 weeks, n=6 per group) or vehicle (n=9). We analysed aortic and renal lesions (Oil-Red-O/hematoxylin and periodic acid-Schiff staining), cellularity (immunohistochemistry of leukocytes and α-smooth muscle actin), fibrotic content (picrosirius red staining), gene expression (real-time quantitative PCR) and NF-κB activity (Southwestern *in situ*).
Results: DMAG treatment reduced the size and the extension of atherosclerotic lesions, without affecting hyperglycemia and lipid profile. It also induced a more stable phenotype of plaque by reducing the amount of lipid, infiltrating leukocytes (macrophages and T-cells) and inflammatory markers (CCL2, CCL5, TNFα and NF-κB), while increasing smooth muscle cell and collagen content. DMAG treatment also improved renal function and reduced renal lesions associated to diabetes, such as mesangial expansion, leukocyte infiltration, inflammation and fibrosis (TGFβ, collagen and fibronectin).
Conclusions: HSP90 inhibition by DMAG restrains the progression of vascular and renal and damage in experimental diabetes.

EAS-0519.
IDENTIFICATION OF THE ORIGIN OF CIRCULATING ENDOTHELIAL PROGENITOR CELLS

T. Fujisawa [1], M. Brittan [1], O. Tura-Ceide [2], A. Hunter [1], A. Mitchell [1], A. Vesey [1], E.M. Skinner [1], C. Medine [1], S. Gallogly [1], P.W.F. Hadoke [1], C. Keith [3], A. Sproul [4], H. Roddie [4], G. McQuaker [5], I. Wilmut [6], N.L. Mills [1]. [1] *BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom;* [2] *Department of Pulmonary Medicine, University of Barcelona, Barcelona, Spain;* [3] *Cytogenetics, Western General Hospital, Edinburgh, United Kingdom;* [4] *Department of Haematology, Western General Hospital, Edinburgh, United Kingdom;* [5] *Bone Marrow Transplant Unit, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom;* [6] *Scottish Centre for Regenerative Medicine, University of Edinburgh, Edinburgh, United Kingdom*

Aim: The discovery of circulating endothelial progenitor cells (EPCs) has stimulated clinical interest in the potential for these cells to treat patients with cardiovascular diseases. The precise origin of the circulating EPCs is unknown and has hampered the development of effective therapies. We hypothesize that circulating EPCs do not originate in the bone marrow, but reside in a niche within the vascular endothelial lining.

Methods: Peripheral blood was used to isolate late endothelial outgrowth cells (EOCs) and early outgrowth cells (CFU-Hill) from patients with allogeneic sex-mismatched bone marrow transplants. Vascular endothelial cells were grown from vascular biopsy with J-shape wire from vein. The origin of cells were analysed by FISH against X and Y chromosome as well as multiplex short tandem repeats (STRs) analysis. Flow cytomerty was used for phenotypic analysis.
Results: EOCs and endothelial cells obtained from vascular biopsies were of recipient genotype by FISH as well as STRs analysis. These cells had typical endothelial morphology and cell surface marker expression by flow cytometry analysis, while CFU-Hill were haematopoietic cells, did not express endothelial markers and had a donor genotype.
Conclusion: Preliminary data suggests true circulating endothelial progenitor cells, capable of forming mature endothelial cells, are derived from the vasculature. These observations challenge the concept of a bone marrow derived endothelial progenitor cell.

EAS-0539.
ANGIOTENSIN-(1-7) AND ANGIOTENSIN-(1-9) INHIBIT VASCULAR SMOOTH MUSCLE CELL GROWTH AND MIGRATION IN VITRO AND VASCULAR REMODELLING IN VIVO

C.A. McKinney [1], S. Kennedy [1], G.S. Baillie [1], G. Milligan [2], S.A. Nicklin [1]. [1] *Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom;* [2] *Institute of Molecular Cell and Systems Biology, University of Glasgow, Glasgow, United Kingdom*

Background: Vascular smooth muscle cell(VSMC) proliferation and migration underlies the pathogenesis of atherosclerosis, vein graft failure and in-stent restenosis. Angiotensin II(AngII), acting via the AT_1R, is integral in these processes. AngII is inhibited by the counter-regulatory axis of the renin angiotensin system, which is centered around the actions of angiotensin-converting-enzyme-2 and the production of Ang-(1-7) and Ang-(1-9), which act via the Mas receptor and AT_2R, respectively. Here we investigated the role of Ang-(1-9) and Ang-(1-7) in primary human VSMC migration and proliferation, and in a mouse model of vascular injury.

Methods: Migration was assessed via scratch assay and proliferation using the MTS-assay. Vascular injury was induced *in vivo* via wire injury to the left carotid artery. Ang-(1-7) and Ang-(1-9) were delivered via osmotic minipump and vascular remodeling quantified at 28 days post-injury.
Results: VSMC migration and proliferation was inhibited by Ang-(1-9) and Ang-(1-7); these effects were selectively blocked by the pharmacological antagonists PD123,319 and A779, respectively, suggesting Ang-(1-9) acts via the AT_2R and Ang-(1-7) via Mas. *In vivo w*ire injury of the mouse carotid artery induced significant neointimal formation(NI) at 28 days post-injury; this was attenuated by Ang-(1-7) and Ang-(1-9) via Mas and the AT_2R, respectively.
Conclusion: These data demonstrate that Ang-(1-7) and Ang-(1-9) inhibit VSMC proliferation and migration *in vitro* and neointimal formation *in vivo* via the AT_2R and Mas receptor, respectively. Here we demonstrate for the first time a direct biological effect of Ang-(1-9) within the vasculature. These findings highlight the potential of Ang-(1-9) and Ang-(1-7) as therapeutic agents in vascular injury.

EAS-0553.
ROLE OF PERIODONTAL PATHOGENS IN INDUCTION OF ATHEROSCLEROSIS IN LDLR-/- MICE

M. Easwaran [1], S. Chukkapalli [1], M. Rivera-Kweh [1], I. Velsko [1], D. Zheng [2], A. Lucas [2], L. Kesavalu [1]. [1] *Periodontology, University of Florida, Gainesville, USA;* [2] *Medicine, University of Florida, Gainesville, USA*

Aim: Periodontal disease (PD) is a polymicrobial chronic inflammatory disease. A distinct pathogenic consortium is found in the subgingival plaque includes *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia* and *Fusobacterium nucleatum*. Atherosclerosis has been linked to PD. We have examined whether oral periodontal pathogens can infect vascular tissues and induce atherosclerotic plaque formation in $LDLR^{-/-}$ mice.

Methods: $LDLR^{-/-}$ mice (Group I) were orally infected with early colonizer *F.nucleatum* for the first 12 weeks followed by late colonizers *P.gingivalis*/*T.denticola*/*T.forsythia* for the remaining 12 weeks. Group II mice were sham-infected. After 8 infection periods (4 days a week every 3rd week for 24 weeks), the mice were euthanized. Periodontal disease parameters like bone loss, antibody levels and oral plaque samples were analyzed. Heart, aorta, spleen, liver, lungs and kidney were evaluated for systemic infection and aorta was examined for atherosclerosis.
Results: *P.gingivalis*, *T.denticola*, *T.forsythia* and *F.nucleatum* genomic DNA were detected in oral plaque samples demonstrating infection of the mice oral cavities. Infected mice serum contain significant levels ($p < 0.001$) of IgG and IgM antibodies. Significant increase in total alveolar bone resorption ($p < 0.001$) was observed. These results support the ability of these oral pathogens to cause PD in the $LDLR^{-/-}$ mice. Genomic DNA from tissue results shows systemic dissemination of these pathogens into the heart, aorta liver, kidney, and lungs. Analysis of atherosclerotic plaque in the aortas is in progress.
Conclusions: This is the first study assessing a causal role of major periodontal pathogens in atherosclerosis in $LDLR^{-/-}$ mice. Supported by R01 DE028020-NIH/NIDCR.