Heart (2004);90:87-91
Interventional magnetic resonance imaging for guiding gene and cell transfer in the heart
I. M. Barbash*, et al.*
Neufeld Cardiac Research Institute, Sheba Medical Centre, Tel-Hashomer, Israel.
BACKGROUND: Interventional magnetic resonance imaging (iMRI) has the potential for guiding interventional cardiac procedures in real time. OBJECTIVES: To test the feasibility of iMRI guided gene and cell transfer to the heart and to monitor myocardial remodelling after myocardial infarction in a rat model. METHODS: The MRI contrast agent GdDTPA, together with either Evans blue dye, or a recombinant adenovirus encoding the LacZ gene, or primary fibroblasts tagged by BrdU, were injected into the myocardium of rats under iMRI guidance. Rats were killed seven days after the injection and the hearts sectioned to identify the blue dye, LacZ expression, or fibroblast presence, respectively. In a parallel study, left ventricular area was measured before and after myocardial infarction and in sham operated rats by T1 weighted MRI and by echocardiography. RESULTS: Location of GdDTPA enhancement observed with iMRI at the time of injection was correlated with Evans blue stain, beta-gal expression, and the primary fibroblast location in histological studies. iMRI and echocardiography measured a comparable increase in left ventricular area at seven and 30 days after myocardial infarction. A good correlation was found between the iMRI and echocardiographic assessment of left ventricular area ($r = 0.70$; $p < 0.0001$) and change in left ventricular area with time ($r = 0.75$; $p < 0.0001$). CONCLUSIONS: The results show the feasibility and efficiency of iMRI guided intramyocardial injections, and the ability to monitor heart remodelling using iMRI. Genes, proteins, or cells for tissue engineering could be injected accurately into the myocardial scar under iMRI guidance.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14676253

J Am Coll Cardiol (2004);43:1915-22
Powerful and controllable angiogenesis by using gene-modified cells expressing human hepatocyte growth factor and thymidine kinase
Y. Hisaka*, et al.*
Institute for Advanced Cardiac Therapeutics, Tokyo, Japan.
OBJECTIVES: This study investigated the possibility of achieving angiogenesis by using gene-modified cells as a vector. BACKGROUND: Although gene therapy for peripheral circulation disorders has been studied intensively, the plasmid or viral vectors have been associated with several disadvantages, including unreliable transfection and uncontrollable gene expression. METHODS: Human hepatocyte growth factor (hHGF) and thymidine kinase (TK) expression plasmids were serially transfected into NIH3T3 cells, and permanent transfectants were selected (NIH3T3 + hHGF + TK). Unilateral hindlimb ischemia was surgically induced in BALB/c nude mice, and cells were transplanted into the thigh muscles. All effects were assessed at four weeks. RESULTS: The messenger ribonucleic acid expression and protein production of hHGF were confirmed. Assay of growth inhibition by ganciclovir revealed that the 50% (median) inhibitory concentration of NIH3T3 + hHGF + TK was 1000 times lower than that of NIH3T3 + hHGF. The NIH3T3 + hHGF + TK group had a higher laser Doppler blood perfusion index, higher microvessel density, wider microvessel diameter, and lower rate

of hindlimb necrosis, as compared with the plasmid- and adenovirus-mediated hHGF transfection groups or the NIH3T3 group. The newly developed microvessels were accompanied by smooth muscle cells, as well as endothelial cells, indicating that they were on the arteriolar or venular level. Laser Doppler monitoring showed that the rate of blood perfusion could be controlled by oral administration of ganciclovir. The transplanted cells completely disappeared in response to ganciclovir administration for four weeks. CONCLUSIONS: Gene-modified cell transplantation therapy induced strong angiogenesis and collateral vessel formation that could be controlled externally with ganciclovir.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15145121

Eur Heart J (2004);25:335-41
The 5A/6A polymorphism of the stromelysin-1 gene and restenosis after percutaneous coronary interventions
P. Hoppmann*, et al.*
Deutsches Herzzentrum Munchen and 1. Medizinische Klinik rechts der Isar, Technische Universitat Munchen, Munchen, Germany.
AIMS: Matrix metalloproteinase stromelysin-1 has been implicated in the process of exaggerated lumen re-narrowing after primarily successful interventions in coronary arteries. We examined the possibility that the 5A/6A promoter polymorphism of the stromelysin-1 gene is associated with restenosis after stenting or percutaneous transluminal coronary angioplasty (PTCA). METHODS AND RESULTS: The study included 3333 consecutive patients with symptomatic coronary artery disease who were treated with stent implantation (n=2857) or PTCA (n=476). Primary end-point was angiographic restenosis, defined as >/=50% diameter stenosis at 6-month follow-up angiography. Restenosis rates were 28.1%, 27.8%, and 29.5% in carriers of the stromelysin-1 genotypes 5A5A, 5A6A, and 6A6A, respectively (P=0.71). The incidence of death or myocardial infarction and the need for revascularization at the site of the intervention due to symptoms or signs of ischaemia in the presence of angiographic restenosis were not significantly different between the genotype groups at 1 year. Separate analysis of the patients who underwent stenting and the patients who were treated with PTCA did not indicate the existence of a treatment type-related association between the 5A/6A polymorphism and restenosis. CONCLUSION: Our data strongly suggest that the 5A/6A polymorphism of the stromelysin-1 gene is not related to angiographic restenosis or the 1-year clinical outcome after interventions in coronary arteries.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14984923

J Am Coll Cardiol (2004);44:644-53
Treatment of acute myocardial infarction by hepatocyte growth factor gene transfer: the first demonstration of myocardial transfer of a "functional" gene using ultrasonic microbubble destruction
I. Kondo*, et al.*
Second Department of Internal Medicine,

OBJECTIVES: We examined whether ultrasonic microbubble destruction (US/MB) enables therapeutic myocardial gene transfer of hepatocyte growth factor (HGF) for acute myocardial infarction (MI). BACKGROUND: Hepatocyte growth factor gene transfer provides cardioprotective effects in MI, which requires direct intramyocardial injection or special vectors. Although US/MB was used in myocardial gene transfer, its feasibility in transfer of a therapeutic gene with non-viral vector remains unknown. METHODS: In a rat model of acute MI, naked plasmid (pVaxl) encoding human HGF (1,500 microg) was infused into the left ventricular (LV) chamber during US/MB (HGF-US/MB) or insonation only (HGF-US) or alone (HGF-alone), while control MI rats received empty pVaxl during US/MB (pVaxl-US/MB). For US/MB, transthoracic intermittent insonation with a diagnostic transducer (1.3 MHz) was performed for 2 min at a peak negative pressure of -2,160 kPa during intravenous 20% Optison. RESULTS: Baseline risk area was comparable among the groups. Immunohistology seven days after treatment revealed significant myocardial expression of HGF protein only in HGF-US/MB. At three weeks, LV weight in HGF-US/MB (0.89 +/- 0.03 g) was significantly lower than those in HGF-alone (1.09 +/- 0.08 g), HGF-US (1.04 +/- 0.07 g), and pVaxl-US/MB (1.04 +/- 0.05 g). Moreover, scar size was significantly smaller (16 +/- 6% vs. 39 +/- 5%, 41 +/- 6%, and 40 +/- 4% of total myocardial circumferential length, respectively), while capillary density (49 +/- 8 vs. 34 +/- 5, 37 +/- 6, and 36 +/- 4 capillaries/high-power field, respectively) and arterial density (37 +/- 7 vs. 15 +/- 9, 18 +/- 4, and 14 +/- 11 arterioles/high-power field, respectively) in the risk area were higher in HGF-US/MB than the other groups. CONCLUSIONS: Ultrasound-mediated microbubble destruction may enable myocardial HGF gene transfer with systemic administration of naked plasmid, which enhances angiogenesis, limits infarction size, and prevents LV remodeling after MI.
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Circulation (2004);110:2066-71
Genetic basis of atherosclerosis: part II: clinical implications
A. J. Lusis*, et al.*
Division of Cardiology, David Geffen School of Medicine at University of California, Los Angeles, USA. jlusis@mednet.ucla.edu.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15466657

Circulation (2004);110:1868-73
Genetic basis of atherosclerosis: part I: new genes and pathways
A. J. Lusis*, et al.*
Department of Medicine/Division of Cardiology, David Geffen School of Medicine at University of California, Los Angeles, USA. jlusis@mednet.ucla.edu
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15451808