

Overall research theme:

Gene and stem cell therapy in ischemic heart disease

Latest update:

March 3, 2003

Senior staff member(s):	Position(s):	Degrees:	E-mail addresses:
Jens Kastrup	Associate professor	MD DMSc	jkastrup@rh.dk
Erik Jørgensen	Chief physician	MD	erikj@rh.dk
Hans E. Johnsen	Associate professor	MD DMSc	haej@herlevhosp.kbhamt.dk

Department/institution/address/telephone/fax:

Cardiac Catheterisation Laboratory 2014, The Heart Centre, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark

Tel.: 3545 2817

Fax: 3545 2705

Characteristics of the research group:

We decided three years ago to establish a research team at Rigshospitalet for evaluation of new molecular diagnostic analyses and treatment regimes for patients with ischemic heart disease. The aim was to establish a broad national and international collaboration with experts within molecular biology research to further develop and implement the newest knowledge in clinical diagnostic cardiology and treatment regimes of patients with both acute and chronic ischemic heart disease.

The aims of the project are in patients with acute and chronic atherosclerotic heart disease:

1. to evaluate two new treatment regimes, gene therapy and bone marrow stem cell therapy
2. to investigate the cellular mechanisms of importance for angiogenesis which are activated in cardiac myocytes during acute and chronic ischemia

Running projects: Titles and abstracts:

Gene therapy in chronic ischemic heart disease

We have established an international multi-centre non-commercial randomized double-blind placebo-controlled gene therapy study, Euroinject One, with the gene encoding for the vascular growth factor VEGF-A₁₆₅ in patients with severe coronary artery disease who could not be treated with conventional coronary by-pass surgery or balloon angioplasty. Guided by an electro-mechanical evaluation by the NOGA system 10 intramyocardial injections of plasmid were placed around and within the tissue area with reversible ischemia previously determined by stress myocardial scintigraphy (SPECT). The study was initiated April 2001 at Department of Cardiology, Rigshospitalet, Copenhagen and the last patient included July 2002. A total of 40 patients received the VEGF-A₁₆₅ plasmid and 40 patients received the placebo plasmid without the gene encoding for VEGF-A₁₆₅. Six centres participated in the study, and a total of 32 of the 80 patients were included in Copenhagen.

Primary endpoint is change of reversible myocardial ischemia on SPECT at three months follow-up. The results have been accepted for presentation as a late breaking trial at The American College of Cardiology Congress April 1, 2003.

Stem cell therapy in chronic ischemic heart disease

In June 2002 we initiated a single centre clinical phase I safety and efficacy study with medical stimulation with G-CSF (granulocyte colony-stimulating factor, Neupogen) of the mobilisation of endothelial progenitor cells from the bone marrow into the blood circulation to develop new blood vessels in ischemic myocardium in patients with severe coronary artery disease, which could not be treated with conventional coronary by-pass surgery or balloon angioplasty. Neupogen has been used for many years in haematology for mobilisation of bone marrow stem cells in patients with leukaemia treated with bone marrow transplantation.

All patients have had the two months follow-up investigations and core lab analyses are ongoing.

Gene and stem cell therapy in chronic ischemic heart disease

The authorities have approved a safety and efficacy study with combined gene therapy with the gene coding for the vascular growth factor VEGF-A₁₆₅ and bone marrow stimulation in 16 patients with severe coronary artery disease who could not be treated with conventional coronary by-pass surgery or balloon angioplasty. The patients will be identical to the patients included in the Euroinject One study and they will have identical gene treatment procedure and follow-up. In addition to the gene therapy, the patients will be treated medically with bone marrow stimulation with Neupogen to increase the circulating numbers of endothelial progenitor cells. The first patient will be treated march 2003.

Stem cells and vascular growth factors in acute coronary syndrom

We are at present evaluating the short- and long-term contribution of endothelial progenitor cells and circulating vascular growth factors in the development of new blood vessels in 20 patients admitted with acute ST-elevation myocardial infarction (STEMI) treated with primary PCI (acute opening of the infarct vessel with balloon angioplasty), and 20 patients with non ST-elevation myocardial infarction (unstable angina pectoris, non-STEMI).

Stem cells differentiation for treatment

We are at present testing the appropriate growth conditions for differentiation of stem cells harvested from the peripheral blood into endothelial progenitor cells and myoblasts. The number of these cells can be increased by in-vitro growth expansion. By this method it is possible to harvest stem cells from a patient, increase the number of progenitor cells and myoblasts, and then deliver the patients own cells to the heart with an injection catheter using the percutaneous approach.

Cellular mechanisms of importance for angiogenesis

The genes encoding for vascular growth factors are present in the genome within the nucleus of the myocytes in the heart. In spite of that, un-blinded clinical gene therapy studies with the gene encoding for VEGF-A₁₆₅ indicate, that it is possible by this short term activating of the introduced vascular gene to induce growth of new vessels in the ischemic myocardium. There is no knowledge about whether the cells own genes coding for the vascular growth factors already are activated in the myocytes in patients with chronic myocardial ischemia. Moreover, it is unknown whether short-time acute myocardial ischemia activates the vascular growth factor genes.

We are investigating the effect of short-term acute and long-term chronic myocardial ischemia on the activation of the genes in myocardial biopsies.

Recent publications related to the projects described above:

J. Kastrup, E. Jørgensen.

Genterapi ved iskæmisk hjertesygdom. Vækstfaktorer og angiogenese/arteriogenese. Ugeskrift for Læger. 2001;1:13-15.

J. Kastrup, E. Jørgensen, V. Drvota.

Vascular growth factor and gene therapy to induce new vessels in the ischemic myocardium. Therapeutic angiogenesis.

Scandinavian Cardiovascular Journal. 2001;35:291-296.

J. Kastrup, E. Jørgensen, V. Drvota, L. Thuesen, H.E. Bøtker, M. Gyöngyösi, D. Glogar, A. Rück, K.B. Islam, C. Sylvén and the Euroinject One group.

Intramyocardial injection of genes by a novel percutaneous technique. Initial safety data in the Euroinject One study.

Heart/Drug 2001;1:299-304.

H. E. Johnsen. Clinical practice and future needs in recombinant human granulocyte colony-stimulating factor treatment: a review of randomised trials in clinical haemato-oncology.

J Int Med Res 2001;29(2):87-99.

S. Serke and H. E. Johnsen. An european reference protokol for quality assesment and clinical validation of autologous haematopoetic blood progenitor and stem cell grafts.
Bone Marrow Transplantation 2001;27(5):463-470.

W. Yongzhong, E Jørgensen, HE Johnsen, J Kastrup.
The clinical impact of endothelial progenitor cells and vascular growth factors in the acute coronary syndrome. A review.
Scandinavian Cardiovascular Journal. 2003;37:1-7.

J. Kastrup. Therapeutic angiogenesis in ischemic heart disease. Gene or recombinant vascular growth factor protein therapy?
Current Gene Therapy. In press.