We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Gene Therapy for Therapeutic Angiogenesis

Rudolf Kirchmair

*Dept. of Internal Medicine, Angiology
Medical University Innsbruck
Austria*

1. Introduction

Cardiovascular diseases still represent the leading cause of death in the western world. Coronary artery disease (CAD) affects over 5% of the US population and is responsible for nearly 7 millions of in-patient procedures every year (1). Peripheral arterial disease (PAD), with a prevalence of 3-30%, also is a very common disease (2). PAD can be classified according to the severity of clinical symptoms into Fontaine-stages I-IV. In Fontaine-stage I patients are clinically asymptomatic and this stage is the most common form of PAD (70-80%). Patients with Fontaine II (10-20%) suffer from intermittent claudication that might be life-style limiting and require therapy like percutaneous transluminal angioplasty (PTA). A smaller portion (3-5%) of PAD patients have critical limb ischemia (CLI) characterized by rest pain (Fontaine III) or ulcer (Fontaine IV). The incidence of CLI is estimated to be 500-1000 per 1 Million but prognosis is very bad. One year after diagnosis only 45 % of patients are alive without major amputation and effective revascularization with relieve of symptoms can only be achieved in 25% of patients. Therefore, new therapeutic strategies are urgently needed for these patients.

2. Preclinical data

Generation of new blood vessels can be achieved by sprouting of new vessels out of the pre-existing capillary plexus (angiogenesis), by generation of new arteries (arteriogenesis) or by circulating endothelial progenitor cells (vasculogenesis) (3). Several factors have been characterized which induce growth of new blood vessels, the most prominent being vascular endothelial growth factor (VEGF) and members of the fibroblast growth factor (FGF) family. In animal models of hindlimb and myocardial ischemia beneficial effects on blood perfusion and blood vessel density of these (and other) factors as well as of progenitor cells could be demonstrated (4) (5). This therapeutic concept was named "therapeutic angiogenesis" and application of angiogenic factors via gene therapy vectors like plasmids or adenoviruses was superior to protein application probably due to longer lasting expression of respective cytokines.

3. Therapeutic angiogenesis: gene therapy trials in PAD patients

Due to promising data in preclinical studies the concept of therapeutic angiogenesis was tested in clinical trials in PAD and CAD patients. While first phase-1 studies in PAD patients were promising phase-II studies in patients with intermittent claudication were negative

(see summary for clinical trials in PAD patients in table 1). Obviously especially patients with CLI respond to therapy with angiogenic factors and gene therapy seems to have a benefit over therapy with respective proteins.

Trial	Factor	Patients	Effects	Reference
Phase-1	VEGF-165 plasmid i.m.	n=6; CLI (Buerger's)	Increase ABI, collaterals; improvement ulcer, pain	Isner et al 1998 (6)
Phase-1	VEGF-165 plasmid i.m.	n=9; CLI	Increase ABI, collaterals; improvement ulcer, pain, walking time	Baumgartner et al 1998 (7)
PREVENT I Phase-1	E2F decoy, bypass graft ex-vivo	n=41; bypass OP	Reduction bypass-stenosis, occlusion and revision	Mann et al 1999 (8)
Phase-1	FGF-2 protein i.a.	n=13; claudication	Increase calf blood flow	Lazarous et al 2000 (9)
Phase-1	FGF-2 protein i.v.	n=24; claudication	No improvement of walking time, proteinuria	Cooper et al 2001(10)
Phase-1	FGF-1 Plasmid i.m.	n=66; CLI	Improvement TcPO2, ABI, pain, ulcer	Comerota et al 2002 (11)
TRAFFIC Phase-2	FGF-2 protein i.a.	n=195; claudication	Improvement walking time, ABI day 90, not 180	Lederman et al 2002 (12)
RAVE Phase-2	VEGF-121 adenovirus i.m.	n=105; claudication	No improvement of walking time	Rajagopalan et al 2003 (13)
Phase-1	VEGF-165 plasmid i.m.	n=21; CLI	Improvement ABI, collaterals, ulcer, pain	Shyu et al 2003 (14)
Phase-1/2	FGF-4 adenovirus i.m.	n=13, CLI	Improvement pain	Matyas et al 2005(15)
PREVENT III Phase-3	E2F decoy, bypass graft ex-vivo	n=1138 bypass operation	Secondary bypass patency improved; primary endpoint (time to bypass occlusion) negative	Conte et al 2006(16)

Trial	Factor	Patients	Effects	Reference
Phase-1/2	HGF plasmid i.m.	n=6; CLI	Improvement pain, ABI, TcPO2, ulcer	Morishita et al 2006(17)
Phase-1/2	FGF-2 gelatine-hydrogel	n=7; CLI	Improvement walking time, TcPO2, ABI, pain	Marui et al 2007(18)
DELTA-1 Phase-2	Del-1 plasmid i.m.	n=105; claudication	No improvement walking time, ABI	Grossman et al 2007(19)
Phase-1	HIF-1 α /VP16 adenovirus i.m.	n=41; CLI	Improvement pain, ulcer	Rajagopalan et al 2007(20)
WALK Phase-2	HIF-1 α /VP16 adenovirus i.m.	n=289 claudication	No difference in walking time	ACC 2009

Abbreviations: CLI, critical limb ischemia; ABI, ankle/brachial index; E2F, transcription factor E2F; HGF, hepatocyte growth factor; Del-1, developmentally regulated endothelial locus 1; HIF-1 α , hypoxia inducible factor-1 α ; Buerger’s, thrombangitis obliterans Winiwater-Buerger; i.m., intra-muscular; i.v., intra-venous; i.a., intra-arterial; TcPO2, transcutaneous oxygen tension

Table 1. Therapeutic angiogenesis in PAD.

Trial	Factor	Patients	Outcome
VEGF PVD Mäkinen et al (22)	VEGF-165 adenovirus or plasmid/liposome i.a. after PTA	n=54; claudication, CLI	Increase of vascular density
Groningen Kusumanto et al (23)	VEGF-165 plasmid i.m.	n=54; CLI	Improvement ABI, ulcers
TALISMAN Nikol et al (24)	FGF-1 plasmid i.m.	n=112; CLI	Reduction of amputations; primary endpoint (healing of ulcers) not reached
HGF-STAT Powell et al (25)	HGF plasmid i.m.	n=106; CLI	Improvement TcPO2
TAMARIS, Phase 3 AHA 2010	FGF-1 plasmid i.m.	n=525; CLI	Primary endpoint (major amputation or death) not reached

Abbreviations: ABI, ankle/brachial index; i.m., intra-muscular; i.v., intra-venous; i.a., intra-arterial; TcPO2, transcutaneous oxygen tension

Table 2. Therapeutic Angiogenesis in PAD:-larger placebo-controlled, double-blinded trials.

The last years several placebo-controlled double-blinded trials have been published which showed beneficial effects in CLI patients after i.m.plasmid gene therapy with VEGF, FGF1 or hepatocyte growth factor (HGF) (Tab. 2). Especially the TALISMAN study could demonstrate a reduction in amputation rate. Regarding potential adverse effects these studies did not show evidence of increase of cancer rates or proliferative retinopathy. (21)

The positive results of the TALISMAN study on reduction of amputation rate and mortality in CLI patients by FGF1 gene therapy was the basis for a large phase 3 study. Over 500 CLI patients were treated with FGF1 gene therapy versus placebo. The primary outcome after 12 months was a combined endpoint of major amputation above the ankle or death. The results of this trial, called TAMARIS, were presented at the AHA meeting, November 2010, in Chicago, USA. There was no difference in mortality and major amputation between FGF1 gene therapy and placebo. Also secondary endpoints were not different and there was no increase in occurrence of malignant diseases or proliferative retinopathy. The difference between the positive results in phase 2 (TALISMAN) and negative results in phase 3 (TAMARIS) were explained by a type-1 error (finding by chance) in the phase-2 study. It will be interesting to see the publication of the TAMARIS trial to further discuss the reasons for this negative trial and the different results of this trial and phase 2 TALISMAN.

4. Therapeutic angiogenesis: gene therapy trials in CAD patients

Several angiogenic cytokines (especially VEGF-A and FGF4) were tested in patients with severe chronic CAD in whom revascularization by angioplasty or bypass surgery was no further option and who suffered from severe angina and limited exercise tolerance (for recent excellent reviews please also see (26, 27). As observed in PAD-patients phase-1 and phase-2 studies showed feasibility of these therapies and signs of bioactivity. Specifically, gene therapy (adenovirus, administered intra-coronary) with FGF4 showed a trend toward increase in exercise time in the AGENT (Angiogenic Gene Therapy) trial and the subsequent phase-2 AGENT 2 trial showed reduction in reversible perfusion defect size (however not statistically significant due to one outlier in the placebo group). The phase-3 AGENT 3 and AGENT 4 trials were stopped early when an interim analysis of the AGENT 3 cohort indicated that the primary endpoint (change in exercise treadmill test after 12 weeks) was unlikely to differ between FGF4 and placebo. A pooled analysis of AGENT 3 and 4 however revealed that women and patients >65 years with severe angina had statistically significant improvement in angina class and exercise test. A subsequent gene therapy trial in women with CAD was stopped, apparently due to slow enrollment.

Also VEGF gene therapy was tested in CAD patients in randomized studies. In the Kuopio Angiogenesis Trial (KAT) no difference in restenosis rate (primary endpoint) was observed after intra-coronary VEGF gene therapy (plasmid liposome or adenovirus), however after 6 months increased myocardial perfusion was found after adenoviral VEGF application. In the Euroinject One study VEGF plasmid was injected intra- myocardial into regions with perfusion defects. The primary endpoint, improvement of myocardial perfusion was not reached, however, VEGF improved regional wall motion score.

For summary of controlled trials on therapeutic angiogenesis in CAD patients see table 3.

5. Future perspectives

The negative results of phase-3 trials AGENT and TAMARIS raise important question about therapeutic angiogenesis and gene therapy. What is the reason that therapeutic angiogenesis with factors like VEGF or FGF did improve outcomes in a variety of animal models but failed to improve human disease? One explanation is that often young animals were used

Trial	Factor	Patients	Effects	Reference
Phase-1/2	VEGF-2 plasmid i.myoc.	n=19; CCS3-4, RA, NR	Improvement angina class	Losordo et al 2002(28)
AGENT Phase-1/2	Adenovirus-FGF4; i.coro.	n=79; CCS2-3	Trend toward increase in exercise time	Grines et al 2002 (29)
AGENT 2 Phase-2	Adenovirus-FGF4; i.coro.	n=52; CCS2-4, RA, NR	Improvement of perfusion defects by SPECT (not sign.)	Grines et al 2003 (30)
VIVA Phase-2	VEGF protein i.coro., i.v.	n=178; RA, NR	Improvement angina class, no effect on exercise time	Henry et al 2003(31)
KAT Phase-2	VEGF-165 adenovirus or plasmid/liposome i.coro.	n=103; stable angina	Improvement in myocardial perfusion, no effect on restenosis	Hedman et al 2003(32)
EUROINJECT- ONE Phase-2	VEGF-165 Plasmid i.myoc.	n=80; CCS3-4, RA, NR	Improvement wall motion, no effect on myocardial perfusion	Kastrup et al 2005(33)
REVASC Open label	Adenovirus VEGF- 121 i.myoc. (thoracotomy)	n=65; CCS2-4, RA, NR	Improvement in exercise time at 26 weeks, not at 12 weeks	Stewart et al 2006(34)
AGENT3/4 Phase-3	Adenovirus-FGF4; i.coro.	n=532; CCS2-4, RA, (AGENT4: NR)	Enrollment stopped after interim analysis, primary endpoint negative. Improvement angina and exercise time in women, older patients with severe symptoms	Henry et al 2007(35)

Abbreviations: CCS, Canadian cardiovascular society; i.coro., intra-coronary; i.myoc., intra-myocardial; i.v., intra-venous; NR, nonrevascularizable; RA, refractory stable angina;

Table 3. Controlled trials on therapeutic angiogenesis in CAD patleis.

whereas in humans usually patients of older age and a variety of co-morbidities are affected. Additionally, transfection efficacy of gene therapy vectors, even of adenoviruses, is lower in humans than in animals and precise dosing of vectors is not possible due to the fact that transgene expression cannot be precisely quantified. Another open question is the selection of gene therapy vectors-adenoviruses usually have adverse effects, especially immunogenicity, whereas plasmid vectors are safe but have low transfection efficacy. Dose and duration of therapy is another question. One dose of a vector that expresses the transgene for days to weeks might not be sufficient to treat a disease that evolved over the time-course of many years. Also patient selection might have been a problem: usually “no-option” patients were included in these studies, e.g. patients with large ischemic ulcers in the case of CLI (Rutherford class 6). Maybe patients with less severe disease, like patients with Rutherford class 5 or patients who would be treated additionally with revascularization procedures would benefit more from therapeutic angiogenesis. Endpoint selection is another critical point as some functional outcome measurements like severity of angina are subjective and might be affected by the placebo effect. Cell-based therapies have shown positive effects in CAD and PAD (36, 37)-maybe a combined therapeutic strategy consisting of cell application and gene therapy with angiogenic factors would result in better outcome.

6. References

- [1] Nikol, S. 2008. Gene therapy of cardiovascular disease. *Curr Opin Mol Ther* 10:479-492.
- [2] Norgren, L., Hiatt, W.R., Dormandy, J.A., Nehler, M.R., Harris, K.A., Fowkes, F.G., Bell, K., Caporusso, J., Durand-Zaleski, I., Komori, K., et al. 2007. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 33 Suppl 1:S1-75.
- [3] Carmeliet, P. 2000. Mechanisms of angiogenesis and arteriogenesis. *Nat Med* 6:389-395.
- [4] Losordo, D.W., and Dimmeler, S. 2004. Therapeutic angiogenesis and vasculogenesis for ischemic disease: part I: angiogenic cytokines. *Circulation* 109:2487-2491.
- [5] Losordo, D.W., and Dimmeler, S. 2004. Therapeutic angiogenesis and vasculogenesis for ischemic disease: part II: cell-based therapies. *Circulation* 109:2692-2697.
- [6] Isner, J.M., Baumgartner, I., Rauh, G., Schainfeld, R., Blair, R., Manor, O., Razvi, S., and Symes, J.F. 1998. Treatment of thromboangiitis obliterans (Buerger's disease) by intramuscular gene transfer of vascular endothelial growth factor: preliminary clinical results. *J Vasc Surg* 28:964-973; discussion 973-965.
- [7] Baumgartner, I., Pieczek, A., Manor, O., Blair, R., Kearney, M., Walsh, K., and Isner, J.M. 1998. Constitutive expression of phVEGF165 after intramuscular gene transfer promotes collateral vessel development in patients with critical limb ischemia. *Circulation* 97:1114-1123.

- [8] Mann, M.J., Whitemore, A.D., Donaldson, M.C., Belkin, M., Conte, M.S., Polak, J.F., Orav, E.J., Ehsan, A., Dell'Acqua, G., and Dzau, V.J. 1999. Ex-vivo gene therapy of human vascular bypass grafts with E2F decoy: the PREVENT single-centre, randomised, controlled trial. *Lancet* 354:1493-1498.
- [9] Lazarous, D.F., Unger, E.F., Epstein, S.E., Stine, A., Arevalo, J.L., Chew, E.Y., and Quyyumi, A.A. 2000. Basic fibroblast growth factor in patients with intermittent claudication: results of a phase I trial. *Journal of the American College of Cardiology* 36:1339-1344.
- [10] Cooper, L.T., Jr., Hiatt, W.R., Creager, M.A., Regensteiner, J.G., Casscells, W., Isner, J.M., Cooke, J.P., and Hirsch, A.T. 2001. Proteinuria in a placebo-controlled study of basic fibroblast growth factor for intermittent claudication. *Vasc Med* 6:235-239.
- [11] Comerota, A.J., Throm, R.C., Miller, K.A., Henry, T., Chronos, N., Laird, J., Sequeira, R., Kent, C.K., Bacchetta, M., Goldman, C., et al. 2002. Naked plasmid DNA encoding fibroblast growth factor type 1 for the treatment of end-stage unreconstructible lower extremity ischemia: preliminary results of a phase I trial. *J Vasc Surg* 35:930-936.
- [12] Lederman, R.J., Mendelsohn, F.O., Anderson, R.D., Saucedo, J.F., Tenaglia, A.N., Hermiller, J.B., Hillegass, W.B., Rocha-Singh, K., Moon, T.E., Whitehouse, M.J., et al. 2002. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. *Lancet* 359:2053-2058.
- [13] Rajagopalan, S., Mohler, E.R., 3rd, Lederman, R.J., Mendelsohn, F.O., Saucedo, J.F., Goldman, C.K., Blebea, J., Macko, J., Kessler, P.D., Rasmussen, H.S., et al. 2003. Regional angiogenesis with vascular endothelial growth factor in peripheral arterial disease: a phase II randomized, double-blind, controlled study of adenoviral delivery of vascular endothelial growth factor 121 in patients with disabling intermittent claudication. *Circulation* 108:1933-1938.
- [14] Shyu, K.G., Chang, H., Wang, B.W., and Kuan, P. 2003. Intramuscular vascular endothelial growth factor gene therapy in patients with chronic critical leg ischemia. *Am J Med* 114:85-92.
- [15] Matyas, L., Schulte, K.L., Dormandy, J.A., Norgren, L., Sowade, O., Grotzbach, G., Palmer-Kazen, U., Rubanyi, G.M., and Wahlberg, E. 2005. Arteriogenic gene therapy in patients with unreconstructable critical limb ischemia: a randomized, placebo-controlled clinical trial of adenovirus 5-delivered fibroblast growth factor-4. *Hum Gene Ther* 16:1202-1211.
- [16] Conte, M.S., Bandyk, D.F., Clowes, A.W., Moneta, G.L., Seely, L., Lorenz, T.J., Namini, H., Hamdan, A.D., Roddy, S.P., Belkin, M., et al. 2006. Results of PREVENT III: a multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. *J Vasc Surg* 43:742-751; discussion 751.
- [17] Morishita, R., Aoki, M., Hashiya, N., Makino, H., Yamasaki, K., Azuma, J., Sawa, Y., Matsuda, H., Kaneda, Y., and Ogihara, T. 2004. Safety evaluation of clinical gene

- therapy using hepatocyte growth factor to treat peripheral arterial disease. *Hypertension* 44:203-209.
- [18] Marui, A., Tabata, Y., Kojima, S., Yamamoto, M., Tambara, K., Nishina, T., Saji, Y., Inui, K., Hashida, T., Yokoyama, S., et al. 2007. A novel approach to therapeutic angiogenesis for patients with critical limb ischemia by sustained release of basic fibroblast growth factor using biodegradable gelatin hydrogel: an initial report of the phase I-IIa study. *Circ J* 71:1181-1186.
- [19] Grossman, P.M., Mendelsohn, F., Henry, T.D., Hermiller, J.B., Litt, M., Saucedo, J.F., Weiss, R.J., Kandzari, D.E., Kleiman, N., Anderson, R.D., et al. 2007. Results from a phase II multicenter, double-blind placebo-controlled study of Del-1 (VLTS-589) for intermittent claudication in subjects with peripheral arterial disease. *Am Heart J* 153:874-880.
- [20] Rajagopalan, S., Olin, J., Deitcher, S., Pieczek, A., Laird, J., Grossman, P.M., Goldman, C.K., McEllin, K., Kelly, R., and Chronos, N. 2007. Use of a constitutively active hypoxia-inducible factor-1 α transgene as a therapeutic strategy in no-option critical limb ischemia patients: phase I dose-escalation experience. *Circulation* 115:1234-1243.
- [21] Tongers, J., Roncalli, J.G., and Losordo, D.W. 2008. Therapeutic angiogenesis for critical limb ischemia: microvascular therapies coming of age. *Circulation* 118:9-16.
- [22] Makinen, K., Manninen, H., Hedman, M., Matsi, P., Mussalo, H., Alhava, E., and Yla-Herttuala, S. 2002. Increased vascularity detected by digital subtraction angiography after VEGF gene transfer to human lower limb artery: a randomized, placebo-controlled, double-blinded phase II study. *Mol Ther* 6:127-133.
- [23] Kusumanto, Y.H., van Weel, V., Mulder, N.H., Smit, A.J., van den Dungen, J.J., Hooymans, J.M., Sluiter, W.J., Tio, R.A., Quax, P.H., Gans, R.O., et al. 2006. Treatment with intramuscular vascular endothelial growth factor gene compared with placebo for patients with diabetes mellitus and critical limb ischemia: a double-blind randomized trial. *Hum Gene Ther* 17:683-691.
- [24] Nikol, S., Baumgartner, I., Van Belle, E., Diehm, C., Visona, A., Capogrossi, M.C., Ferreira-Maldent, N., Gallino, A., Wyatt, M.G., Wijesinghe, L.D., et al. 2008. Therapeutic angiogenesis with intramuscular NV1FGF improves amputation-free survival in patients with critical limb ischemia. *Mol Ther* 16:972-978.
- [25] Powell, R.J., Simons, M., Mendelsohn, F.O., Daniel, G., Henry, T.D., Koga, M., Morishita, R., and Annex, B.H. 2008. Results of a double-blind, placebo-controlled study to assess the safety of intramuscular injection of hepatocyte growth factor plasmid to improve limb perfusion in patients with critical limb ischemia. *Circulation* 118:58-65.
- [26] Gupta, R., Tongers, J., and Losordo, D.W. 2009. Human studies of angiogenic gene therapy. *Circ Res* 105:724-736.
- [27] Beohar, N., Rapp, J., Pandya, S., and Losordo, D.W. 2010. Rebuilding the damaged heart: the potential of cytokines and growth factors in the treatment of ischemic heart disease. *J Am Coll Cardiol* 56:1287-1297.

- [28] Losordo, D.W., Vale, P.R., Hendel, R.C., Milliken, C.E., Fortuin, F.D., Cummings, N., Schatz, R.A., Asahara, T., Isner, J.M., and Kuntz, R.E. 2002. Phase 1/2 placebo-controlled, double-blind, dose-escalating trial of myocardial vascular endothelial growth factor 2 gene transfer by catheter delivery in patients with chronic myocardial ischemia. *Circulation* 105:2012-2018.
- [29] Grines, C.L., Watkins, M.W., Helmer, G., Penny, W., Brinker, J., Marmur, J.D., West, A., Rade, J.J., Marrott, P., Hammond, H.K., et al. 2002. Angiogenic Gene Therapy (AGENT) trial in patients with stable angina pectoris. *Circulation* 105:1291-1297.
- [30] Grines, C.L., Watkins, M.W., Mahmarian, J.J., Iskandrian, A.E., Rade, J.J., Marrott, P., Pratt, C., and Kleiman, N. 2003. A randomized, double-blind, placebo-controlled trial of Ad5FGF-4 gene therapy and its effect on myocardial perfusion in patients with stable angina. *J Am Coll Cardiol* 42:1339-1347.
- [31] Henry, T.D., Annex, B.H., McKendall, G.R., Azrin, M.A., Lopez, J.J., Giordano, F.J., Shah, P.K., Willerson, J.T., Benza, R.L., Berman, D.S., et al. 2003. The VIVA trial: Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis. *Circulation* 107:1359-1365.
- [32] Hedman, M., Hartikainen, J., Syvanne, M., Stjernvall, J., Hedman, A., Kivela, A., Vanninen, E., Mussalo, H., Kauppila, E., Simula, S., et al. 2003. Safety and feasibility of catheter-based local intracoronary vascular endothelial growth factor gene transfer in the prevention of postangioplasty and in-stent restenosis and in the treatment of chronic myocardial ischemia: phase II results of the Kuopio Angiogenesis Trial (KAT). *Circulation* 107:2677-2683.
- [33] Kastrup, J., Jorgensen, E., Ruck, A., Tagil, K., Glogar, D., Ruzyllo, W., Botker, H.E., Dudek, D., Drvota, V., Hesse, B., et al. 2005. Direct intramyocardial plasmid vascular endothelial growth factor-A165 gene therapy in patients with stable severe angina pectoris A randomized double-blind placebo-controlled study: the Euroinject One trial. *J Am Coll Cardiol* 45:982-988.
- [34] Stewart, D.J., Hilton, J.D., Arnold, J.M., Gregoire, J., Rivard, A., Archer, S.L., Charbonneau, F., Cohen, E., Curtis, M., Buller, C.E., et al. 2006. Angiogenic gene therapy in patients with nonrevascularizable ischemic heart disease: a phase 2 randomized, controlled trial of AdVEGF(121) (AdVEGF121) versus maximum medical treatment. *Gene Ther* 13:1503-1511.
- [35] Henry, T.D., Grines, C.L., Watkins, M.W., Dib, N., Barbeau, G., Moreadith, R., Andrasfay, T., and Engler, R.L. 2007. Effects of Ad5FGF-4 in patients with angina: an analysis of pooled data from the AGENT-3 and AGENT-4 trials. *J Am Coll Cardiol* 50:1038-1046.
- [36] Schachinger, V., Erbs, S., Elsasser, A., Haberbosch, W., Hambrecht, R., Holschermann, H., Yu, J., Corti, R., Mathey, D.G., Hamm, C.W., et al. 2006. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 355:1210-1221.

- [37] Walter, D.H., Krankenberg, H., Balzer, J.O., Kalka, C., Baumgartner, I., Schluter, M., Tonn, T., Seeger, F., Dimmeler, S., Lindhoff-Last, E., et al. 2011. Intraarterial Administration of Bone Marrow Mononuclear Cells in Patients With Critical Limb Ischemia: A Randomized-Start, Placebo-Controlled Pilot Trial (PROVASA). *Circ Cardiovasc Interv* 4:26-37.

IntechOpen

IntechOpen

Gene Therapy - Developments and Future Perspectives

Edited by Prof. Chunsheng Kang

ISBN 978-953-307-617-1

Hard cover, 356 pages

Publisher InTech

Published online 22, June, 2011

Published in print edition June, 2011

The aim of this book is to cover key aspects of existing problems in the field of development and future perspectives in gene therapy. Contributions consist of basic and translational research, as well as clinical experiences, and they outline functional mechanisms, predictive approaches, patient-related studies and upcoming challenges in this stimulating but also controversial field of gene therapy research. This source will make our doctors become comfortable with the common problems of gene therapy and inspire others to delve a bit more deeply into a topic of interest.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Rudolf Kirchmair (2011). Gene Therapy for Therapeutic Angiogenesis, Gene Therapy - Developments and Future Perspectives, Prof. Chunsheng Kang (Ed.), ISBN: 978-953-307-617-1, InTech, Available from: <http://www.intechopen.com/books/gene-therapy-developments-and-future-perspectives/gene-therapy-for-therapeutic-angiogenesis>

INTech
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](https://creativecommons.org/licenses/by-nc-sa/3.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen