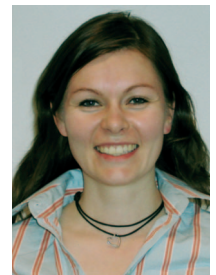


Werner Risau-Preis für Marika Kärkkäinen

Wissenschaftliche Laufbahn:

Scientific career:

- 1993–1998 Student in the University of Kuopio, Finland
Master's thesis on "Expression and effects of vascular endothelial growth factor in transgenic mice" carried out in the laboratory of Dr. Kari Alitalo, Professor of the Finnish Academy of Sciences, University of Helsinki
- 1998 Master of Science (majoring in biochemistry)
Department of Biochemistry and Biotechnology, University of Kuopio, Finland
- 1998–2001 Graduate student at the Helsinki Biomedical Graduate School
Research project in Dr. Alitalo's group: "Characterization of VEGFR-3 mutations in human lymphedema"
- 2002 Doctor of Philosophy, Medical Faculty, University of Helsinki, Finland
Doctoral Dissertation: "VEGFR-3 in Primary Lymphedema" Opponent: Professor Peter Carmeliet, University of Leuven, Belgium
- 2003– present Researcher of the Finnish Academy of Sciences (2-year position)
Research project: "Development of growth factor therapy for human lymphedema"



Prizes and Personal grants:

- 2004 LRF – Andrew Moisoff Young Investigator Poster Award Recognition at the GRC on "Molecular Mechanisms in Lymphatic Disease & Function"
- 2003 A prize for the best biomedical thesis, University of Helsinki
- 2001 Personal grants from Ella and Georg Ehrnrooths Foundation and Paulo Foundation
- 2000 Personal grants from Research and Science Foundation of Farnos and Emil Aaltonen Foundation
- 1999 Personal grants from Ida Montini Foundation and Finnish Cultural Organizations
- 1998 Personal grant from Finnish Cancer Organizations
- 1998 A student prize for an excellent poster presentation at the Xth International Vascular Biology Meeting, Cairns, Australia

Vascular endothelial growth factor C (VEGF-C) is required for proper lymphatic development

The cardiovascular system consists of a circulatory system, in which the heart pumps blood via arteries, capillaries and veins, serving nutrients and oxygen to all cells in the body. A less well known lymphatic vascular system comprises a separate vessel network that also permeates most organs in the body. Lymphatic vessels begin as blind-ended vessels from the periphery, and they have an important role in draining

the extravasated fluid and immune cells through the lymph nodes back to the blood circulation. Abnormal function of lymphatic vessels is associated with several diseases, such as tumor metastasis and lymphedema. Development of methods for local and controlled induction or inhibition of lymphangiogenesis is thus of major importance for the treatment of such diseases.

VEGF-C and a related growth factor, VEGF-D have been shown to stimulate the lymphatic endothelium via their VEGFR-3 receptor. In our latest project, we have analyzed embryonic development of the lymphatic system in mice deficient in VEGF-C. We were able to show that VEGF-C is the paracrine factor that triggers the sprouting of the lymphatic endothelial cells from the embryonic veins. VEGF-C is indispen-

sable in this process, and cannot be compensated by any another ligand of the VEGF family. Our findings are consistent with the theory proposed a century ago by Dr. Sabin, namely that the lymphatic vessels originate from the venous endothelium. Our results also provide novel mechanistic insight into this basic biological process whereby lymphatic endothelial cells are separated from the blood vasculature. Strikingly, mice heterozygous for Vegfc also showed defects in the lymphatic vasculature and they exhibited cutaneous lymphatic hypoplasia and lymphedema. These results indicate that VEGF-C is the factor required for embryonic lymphangiogenesis, and that it dose-dependently sustains normal lymphatic vasculature. The importance of the VEGF-C/VEGFR-3 signal-

ing system in the proper formation of the lymphatic vasculature has also been implicated in human disease. Recently, in collaboration with Dr. Ferrell and Dr. Finegold (Pittsburgh), we have shown that heterozygous inactivation of VEGFR-3 tyrosine kinase activity leads to inherited, congenital lymphedema (Milroy's disease). The swelling of the extremities in these patients is caused by a hypoplastic cutaneous lymphatic network and insufficient lymphatic drainage. Similar inactivating VEGFR-3 mutation also results in lymphedema in the Chy mice, which serve as a mouse model for Milroy's disease. Currently, there is no known cure for lymphedema, which has mainly been treated by physiotherapy and by compression garments. We have addressed the question whether VEGF-C over-

expression can be used to modulate the lymphatic vasculature in situations in which there is insufficient lymphatic drainage. We have shown that viral VEGF-C gene transfer to the skin induces growth of cutaneous lymphatic vessel network in the Chy lymphedema mice. In collaboration with Dr. Rockson (Stanford), we have also shown that VEGF-C protein therapy is applicable to secondary lymphedema in a rabbit model. We are now continuing the work to develop novel pro-angiogenic and pro-lymphangiogenic therapies for vascular disorders. These therapeutic approaches will be developed further in animal models and the first clinical trials have been planned to be carried out in near future.

Selected Publications:

- Karkkainen MJ, Haiko P, Sainio K, Partanen J, Taipale J, Petrova T, Jeltsch M, Jackson DG, Talikka M, Rauvala H, Betsholtz C and Alitalo K. VEGF-C is required for sprouting of the first lymphatic vessels from embryonic veins. *Nat. Immunol.* **5**, 74-80 (2004)
- Szuba A, Skobe M, Karkkainen MJ, Shin WS, Beynet DP, Rockson NB, Dakhil N, Spilman S, Goris ML, Strauss HW, Quertermous T, Alitalo K and Rockson SG. Therapeutic lymphangiogenesis with VEGF-C. *FASEB J.* **16**, 1985-1987 (2002)
- Saaristo, A, Veikkola T, Tammela T, Enholm B, Karkkainen MJ, Pajusola K, Bueler H, Ylä-Herttua S and Alitalo K. Lymphangiogenic gene therapy without blood vascular side-effects. *J. Exp. Med.* **196**, 719-730 (2002)
- Karkkainen MJ, Saaristo A, Jussila L, Karila KA, Lawrence EC, Pajusola K, Bueler H, Eichmann A, Kauppinen R, Kettunen MI, Ylä-Herttua S, Finegold DN, Ferrell RE and Alitalo K. A model for gene therapy of human hereditary lymphedema. *Proc. Natl Acad. Sci. USA.* **98**, 12677-12682 (2001)
- Ijijn K, Karkkainen MJ, Lawrence EC, Kimak MA, Uutela M, Taipale J, Pajusola K, Alhonen L, Halmekytö M, Finegold DN, Ferrell RE, and Alitalo K. VEGFR3 gene structure, regulatory region and sequence polymorphisms. *FASEB J.* **15**, 1028-1036. (2001)
- Karpanen T, Egeblad M, Karkkainen MJ, Kubo H, Jackson DG, Ylä-Herttua S, Jäättelä M and Alitalo K. Vascular endothelial growth factor C promotes tumor lymphangiogenesis and intralymphatic tumor growth. *Cancer Res.* **61**, 1786-1790. (2001)
- Irrthum A, Karkkainen MJ, Devriendt K, Alitalo K and Vikkula M. Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyrosine kinase. *Am. J. Hum. Genet.* **67**, 295-301. (2000)
- Karkkainen MJ, Ferrell RE, Lawrence EC, Kimak MA, Levinson KL, McTigue MA, Alitalo K and Finegold DN. Missense mutations interfere with vascular endothelial growth factor receptor-3 signaling in primary lymphoedema. *Nat. Genet.* **25**, 153-159 (2000)
- Karkkainen MJ, Mäkinen T and Alitalo K. Lymphatic Endothelium: a new frontier of metastasis research. *Nat. Cell. Biol.* **4**, E2-E5. (2002) (review)
- Karkkainen MJ, Jussila L, Ferrell RE, Finegold DN and Alitalo K. Molecular regulation of lymphangiogenesis and targets for tissue oedema. *Trends Mol. Med.* **7**, 18-22. (2001) (review)

Personalien

Die DGZ begrüßt folgende neue Mitglieder:

Tanja BARENDZIAK (Bremen), Dr. Renate BURGEMEISTER (Bernried), Dr. Eva DECKER (Freiburg), Florian EICH (Frankfurt), Dr. rer. nat. Cordula ENENKEL (Berlin), Dr. Nicole FÖGER (Heidelberg), Dr. Stefan GEIMER (Bayreuth), Joanna HERMAINSKI (Berlin), Dr. Anne HOLZ (Giessen), Dr. Mark KAIL (Münster), Cand. med. vet. Michael KRAHN (Everswinkel), Dr. Songjie LIU (Göttingen), Dr. Hans-Michael MERZENDORFER (Osnabrück), Hanno MÜLLER (Marburg), Dr. Klemens ROTTNER (Braunschweig), Dr. Ansgar SANTEL (Berlin), Ute SCHMIDT (Heidelberg), Harald STACHELSCHIED (Berlin), Dr. Carsten THEISS (Bochum), Samuel WAGNER, M.Sc. (Stockholm)

Wer kann uns helfen? Von den unten aufgeführten Mitgliedern fehlen uns die aktuellen Adressen. Wenn jemand uns diesbezüglich weiterhelfen kann, bitten wir um Mitteilung an unser Sekretariat. Wir sind für jeden Hinweis dankbar. Vielen Dank für Ihre Mithilfe!

Bayer Michael, Bouterfa Hakim, Boxler-Baldomà Carmen, Brand Margrit, Brüntrup Ines Maria, Buchner Klaus, Bumann Johann, Buniatian Gayane, Cerina Ivica, Donoso-Lui Gerda, Dresbach Thomas, Dressler Cathrin, Fernow Inga, Francz Pal Istvan, Friedrich Eckhard, Friedrich Karlheinz, Gawlitta Wolfgang, Gossiau Andreas, Graupner G., Grimme Susanne, Gruner Karl Reinhold, Grunwald Ingo, Haas Ingrid, Halle Jörn-Peter, Hensel Gabriele, Herbst Detlev, Hippe Annette, Horstmann Hans-Joachim, Horstmeyer Angelika, Klein Christoph L., Klein Markus, Klöhn Peter-Christian, Knoll Gerhard, Krafft Thorsten, Kraus Michael, Krüger Bernd, Küchler Michael, Lederer Marcell, Leichter Michael, Liedvogel Bodo, Loges Sonja, Meister-ernst Michael, Menkel Annette Regina, Michel Caroline, Mietchen Daniel, Neugebauer Dorothea-Ch., Neumann-Giesen Carolin, Otto Andrea M., Paulus Gerd, Peschke Matthias, Poppe Robert, Ribicki Robert, Rose Horst, Schambony Alexandra, Schwarz Gerd, Stein Jörg Andreas, Stratmann Rembert, Waldvogel Horst, Wiedemann Agnes, Wittenmayer Nina, Wittmann-Liebold Brigitte, Wolff Jan, Yalkinoglu A. Özkan, Zobiack Nicole.

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