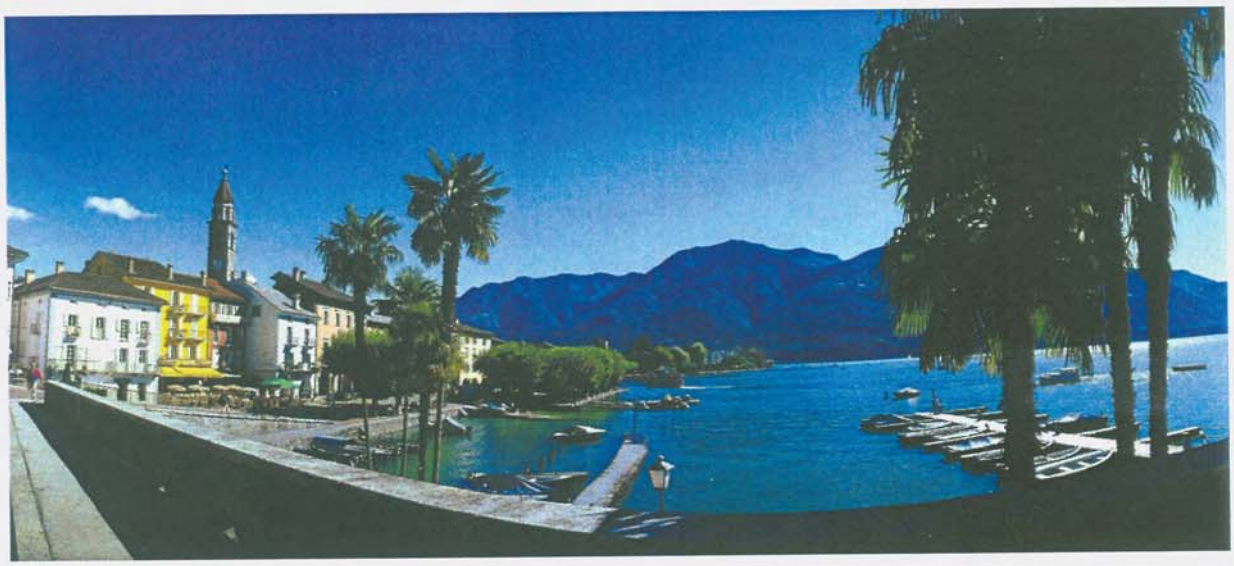
5th International Conference on Tumor-Host Interaction and Angiogenesis



Centro Stefano Franscini, Monte Verità, Ascona, Switzerland

June 2 – 5, 2013

http://www.unifr.ch/med/mva2013

Organizers:

Kari Alitalo, Tatiana Petrova and Curzio Rüegg

UNIL | Université de Lausanne

UNIVERSITAS FRIBURGENSIS

UNIVERSITY OF HELSINKI

Centro Stefano Franscini
Swiss Federal Institute of Technology Zurich

Sunday, June 2, 2013

16 :00-16 :50	*Welcome reception*
17 :00-17 :15	Introduction **Curzio Rüegg**
17 :15-18 :45	**Session 1** **KEYNOTE OPENING LECTURES** Discussion leader : Tatiana Petrova
17 :15-18 :00	Genetic modifiers and micro-environmental control of tumor invasiveness **Doug Hanahan**, Lausanne (p.16)
18:00-18:45	Targeting endothelial metabolism: principles and strategies **Peter Carmeliet**, Leuven (p. 5)
19:00	*Dinner*

Monday, June 3, 2013

8:15-8:30	Welcome address by the Centro Stefano Franscini **Chiara Cometta**
8:30-12:15	**Session 2** **TUMOR ANGIOGENESIS AND LYMPHANGIOGENESIS** Discussion leaders: Kari Alitalo and Oriol Casanovas
8:30-9:00	VEGF signaling in the tumor vasculature **Lena Claesson-Welsh,** Uppsala (p. 8)
9:00-9:15	Hypoxia induces VEGF-C expression in metastatic tumor cells via a HIF-1a-independent translation-mediated mechanism **Barbara Garmy-Susini**, Toulouse (p. 43)
9:15-9:45	Principles of vascular pattern generation in developmental and tumour angiogenesis **Holger Gerhardt,** London (p. 15)
9:45-10:15	Molecular Targeting of Tumor Vasculatures **Gou Young Koh**, Daejeon (p. 19)
10:15-10:45	*Coffee break*
10:45-11:15	Combinatorial targeting of endothelial growth factor pathways **Kari Alitalo**, Helsinki (p. 3)

Molecular targeting of tumor vasculatures

Gou Young Koh and LVBSC members

Laboratory of Vascular Biology and Stem Cells, Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Korea

Tumor vessels are activated, destabilized, malformed, enlarged, intussusceptive, leaky and highly branched vessels with numerous vascular remodeling. These features are mainly result of abnormally high level of VEGF-A in the tumor microenvironment, and blockade of VEGF-A has been shown to suppress the pathological characteristics of tumor vessels. However, the vascular suppression by blockade of VEGF-A/VEGFR2 signaling frequently causes promotions of rebound hypoxia, micro-invasion, drug-resistance and metastasis, which are challenging to treat cancers using current anti-VEGF therapy. Since angiopoietin-2 (Ang2) plays supportive roles on the VEGF-A induced pathological vascular remodeling and Ang2 level is also high in the tumor microenvironment, single blockade of Ang2 or simultaneous blockade of VEGF-A and Ang2 are currently developed and tested in experimental and clinical settings. Nevertheless, such anti-angiogenic therapy against the tumor progression still seems ineffective, selective and limited in clinics. Here, we found that RhoX, one of Rho family proteins, is selectively expressed in endothelial cells of tumor vessels, and plays a central role in vessel stabilization. Compared to control mice, RhoX deficient mice showed delayed tumor progression, reduction of vascular density and tumor metastasis in the xenograft and primary tumor animal models. The RhoX deficient mice strikingly displayed severe vascular leakage and tumor necrosis, which could be due to marked drop-out of perivascular cells and profound shut-down of tumor vessels. Specific aptide-liposomal delivery of siRNA targeting RhoX could recapitulate the antitumor effect and the vascular shut-down effects shown in RhoX deficient mice. More importantly, blockade of VEGF-A/VEGR2 signaling by administration of VEGF-Trap into RhoX deficient mice showed enhanced almost completely suppression of tumor progression and metastasis without any potentiation of the side effects. Our data collectively suggest that concomitant blockade of VEGF-A and RhoX could be a novel and effective targeting for dual suppression and shut-down of tumor vasculatures.