# Molecular/Cancer Biology Laboratory



Kari Alitalo

#### Berndt Enholm

Do pro-angiogenic factors affect the progression of prostate cancer ? Overexpression of pro-angiogenic factors and oncogenes in mouse prostate provides a model to answer this question.





# Marko Uutela

## Novel VEGFs

I am studying two new vascular endothelial growth factors discovered during our collaborative work with Ulf Eriksson. I have sequenced their cDNA clones and mapped their chromosomal locations using fluorescence in situ hybridization. At the moment I am studying whether these factors bind to known VEGF-receptors.

Several knockout and chimera studies implicate Tie-2 and the related Tie-1 receptor in cell survival. B-Raf knockout mice show a similar phenotype as Tie-2 null mice. We have studied the involvement of B-Raf in Tek signalling using biochemical methods.

development of

vasculature

I am also inter-

ested in how

the lymphatic

vasculature

develops and

how it is regu-

lated during

adult life.

Eola Valdre

VEGF-C knock-out mice and angiogenesis inhibtors



#### Lotta Jussila Transgenic mouse models for VEGFR-3

I use transgenic mouse models to characterize the role of VEGFR-3.

Fig. A 13 day mouse embryo having ß-gal gene (blue) marker in lymphatic vessels.

#### Terhi Kärpänen

#### In-vivo studies with recombinant proteins 3

I am studying the role of the VEGF receptor-3 during avian embryonic development and in angiogenesis in adult mice. In these experiments I use recombinant soluble VEGFR-3-Ig fusion proteins for functional blocking of the VEGFR-3 signalling pathway. I am also interested in the biological function and the VEGFR-1 binding determinants of VEGF-B. Fig. Insect cells expressing VEGF-B. 🥺

# Niklas Ekman, Elena Arighi and Iiro Rajantie Functional analysis of the Bmx tyrosine kinase

The Bmx (Bone Marrow tyrosine kinase in chromosome X) is a member of the Tec family of nonreceptor tyrosine kinases. The Bmx mRNA has been detected in granulocytes and in certain endothelial cells, but very little has been known about the function of this protein. The goal of the present study

My main project is the gene disruption study of VEGF-C, including conditional knock-out as well as use of the zebrafish in developmental and evolutionary studies of angiogenesis. I am also characterizing the effects of endothelial-specific angiogenesis inhibitors on the proliferation, migration and death of endothelial cells.

Taija Mäkinen

Neuropilin and

lymphatic

I am studying

the role of the

axon guidance

molecule

Neuropilin-1 in

angiogenic pro-

cesses.

#### is to understand the signalling cascades involving Bmx and the role of the protein in differentiating hematopoietic cells. Both cell culture models and in vivo mouse models are used for this purpose.

The human body consists of several trillion cells. To avoid chaos, all these cells have to communicate. A simple model of communication is shown in Fig. 1. Cell A sends a message by producing a signalling molecule. Cell B recognizes the signalling molecule, because it has receptors, that fit to the signalling molecule like a key to its keyhole ("receptor binding"). Cell B responds to the message by changing its behavior. Growth factors are such signalling molecules. Hundreds of different growth factors are known and everyone delivers a special message from one cell to another.



#### Angiogenesis Research

Our laboratory works on growth factors, that regulate the development and function of blood vessels and lymphatic vessels. After reaching a size of several millimeters a developing embryo can only continue growing by establishing a circulatory system that supplies all of its cells with oxygen and nutrients. Blood vessels consist mainly of endothelial cells and are formed by two different mechanism's: 1. Vasculogenesis and 2. Angiogenesis.

#### Vasculogenesis

The earliest blood vessels of an embryo form by vasculogenesis. Vasculogenesis is the differentiation of endothelial cells from precursor cells (angioblasts). Angioblasts aggregate and form blood islands (Fig. 2). Cells at the periphery become endothelial cells; cells in the centre



Angiogenesis is the sprouting of new blood vessels from preexisting vessels (Fig. 3). Angio-genesis is responsible for the vascularization of developing organs like the brain, kidney Fig. 3 and limbs. The most important growth factor that makes

blood vessels grow is Vascular Endothelial Growth Factor (VEGF). VEGF binds two different receptors: VEGF receptor-1 (VEGFR-1) and VEGF receptor-2 (VEGFR-2).

## Lymphangiogenesis

The lymphatic system develops later than the cardiovascular system. All lymphatic vessels arise by angiogenesis. The first lymphatic vessels sprout from the venous compartment of the circulatory system. The only known growth factor, that stimulates the growth of lymphatic vessels was cloned in our laboratory: VEGF-C. VEGF-C binds to VEGF receptor-2 and VEGF receptor-3 (VEGFR-3).

#### Blood vessel growth in adults

The blood vessels of a fully developed organism only need to grow under special circumstances, e.g. in wound healing. Blood vessel growth in adults occurs only by angiogenesis.

#### Cancer and angiogenesis

Not only embryos, but also tumors need blood vessels to be able to grow. A tumor usually is only dangerous if it can attract blood vessels (Fig. 4). On the other hand if it was possible to stop blood vessel growth, one could stop tumor growth. Tumor therapy with anti-angiogenic substances is one of the hottest topics in biomedical research and clinical trials have started.



# Michael Jeltsch

### Structural basis of biological activity

VEGF induces blood vessel growth, whereas VEGF-C induces lymphatic vessel growth. Where are the structural differences and similarities underlying the biological function?



#### Karri Paavonen

VEGF-C and VEGFR-3 in inflammatory states I study the role and expression of growth factor receptors in angiogenesis involved in acute and chronic inflammatory states.

## Kristiina Iljin

Tie-1 is one of the five endothelial cell specific receptor tyrosine kinases. I am studying



# Talking Cells

the regulation of the Tie-1 gene. My aim is to characterize DNA elements from the Tie-1 promoter region needed for the activity and endothelial cell specificity of this gene.



become blood cells. Vasculogenesis forms the early heart rudiment, the major blood vessels and the vessels of lung, spleen and pancreas.

#### Reija Valtola

VEGF-C and VEGF receptor-3 expression in breast cancer My studies focus on VEGFR-3 and

VÉGF-C expression in breast cancer. I am also evaluating biological activities of VEGFR-3- and VÉGF-C antibodies. Fig. VEGFR 3 positive vessels in breast cancer



#### Taina Partanen & Anne Saaristo

# Expression studies

We are analyzing the distribution of VEGF receptor-3 and VEGF-C in normal fetal and adult tissues and tumors by immunohistochemistry.

# Juha Laurén

Virtual cloning in silico Apart from web surfing and @-mailing (which occupies me almost totally) I am doing virtual clonings.

# Joni Turunen

ALK-1 and blood vessel formation

I am studying the role of ALK-1 in blood vessel formation. ALK-1 is a TGF- $\beta$  superfamily receptor and inactivating mutations of ALK-1 in humans cause hereditary hemorrhagic telangiectasia.



# Tanja Veikkola

How do VEGF receptor-2 and VEGF receptor-3 function in live animals?

We aim to characterize the different functions of VEGFR-2 and VEGFR-3 in the context of whole organism (as opposed to cell culture) by targeted overexpression of Orf virus VEGF (binds only VEGFR-2), mutant VEGF-C (binds only VEGFR-3) and VEGF-D (binds both VEGFR-2 and VEGFR-3) in the skin of transgenic mice.



#### Marika Kärkkäinen

VEGFs in malignant tumors and metastases/VEGF receptor-3 mutations in hereditary lymphedema

I study the role of angiogenic growth factors in breast cancer its metastases by using transgenic mouse models. In my other project, I am characterizing the role of VEGFR-3 mutations in hereditary lymphedema.

Fig. Association of VEGFR-3 mutants with hereditary lymphedema



#### Selected references

- Dumont et al., Cardiovascular Failure in Mouse Embryos Deficient in VEGF Receptor-3. Science 282: 946-49, 1998.
- **Jeltsch et al.**, Hyperplasia of Lymphatic Vessels in VEGF-C Transgenic Mice. Science 276: 1423-25, 1997.
- Korpelainen & Alitalo, Signaling Angiogenesis and Lymphangiogenesis. Current Opinion in Cell Biology 10: 159-64, 1998.

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