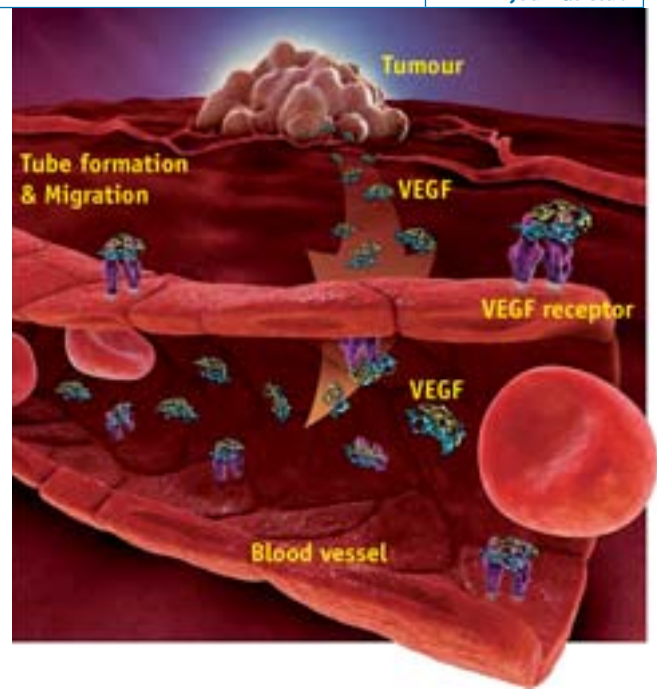
Angiogenesis in Helsinki

"Metastasis is the Challenge"



Stopping tumours from growing rather than eliminating them is how Kari Alitalo sees the battle against cancer being won. Since the attraction of new blood vessels is an important prerequisite for a small tumour to grow into a big one, he and his group have, therefore, been digging deep into the mechanisms underlying angiogenesis. But that's not all...

"Angiogenesis is the growth of blood vessels from pre-existing ones," explains Kari Alitalo. But why has he, one of Europe's leading cancer biologists, dedicated his career to uncovering its secrets? He believes that by halting angiogenesis in small tumours, he can stop them from growing into big ones. And not without reason. Just like any other multicellular structure, tumours need a blood supply to grow. Without new blood vessels, tumours do not grow bigger than a few millimetres across.

Blocking the receptor

As Director of the Centre of Excellence in Cancer Biology at the Finnish Academy Medical Research Council in Helsinki, Alitalo and his group of 30 researchers has done much to characterise the molecular biology and progression of tumours. Focussing on the molecular mechanisms that drive angiogenesis, lymphangiogenesis (the growth of lymphatic vessels) and the molecular biology of colon cancer, the group has stationed itself on the front line in the fight against cancer.

"We all get our vasculature during embryogenesis, in the process of angiogenesis which finishes soon after birth." In embryos, angiogenesis is usually triggered by oxygen deficiency. Unfortunately, it can also happen in developing tumours. Hypoxia inducible factors (HIFs) are transcription factors that are activated when cells sense low oxygen concentrations. They stimulate the transcription of many genes, including vascular endothelial growth factor (VEGF), which is secreted by tumour cells and binds to dedicated VEGF receptors (VEGFRs) on the surface of nearby blood vessel walls. It is these VEGFRs, after stimulation by VEGFs, that cause blood vessels to branch out. This gives tumours a blood supply; they grow larger and can become malignant.

Judah Folkman, an American doctor and scientist, was an early pioneer in the field of angiogenesis. He realised that without new vessels, tumours stay small. Once his work was accepted and understood, researchers tried to block the growth of new blood vessels to halt tumour progression. This approach worked pretty well but not completely, with VEGF monoclonal antibodies (developed by Napoleone Ferrara and colleagues at Genentech, California) successfully blocking angiogenesis. Already proved to be effective in the treatment of several types of cancer, these antibodies are available and approved for use under the trade name Avastin.

Kari Alitalo (with sunglasses) and team members

But now, together with an international team of collaborators, Alitalo's group has showed that blocking a VEGF receptor, VEGFR-3, effectively does the same job (Tammela *et al.*, *Nature* 454: 656-60). Antibodies targeting VEGFRs have not yet entered the commercial market but look set to make their debut soon. "Advanced clinical trials have been carried out with antibodies against VEGFR-2 and it is in this setting that we will embark upon clinical studies with antibodies, which block VEGFR-3." These trials will test combination therapies (the simultaneous use of more than one antibody) since preclinical studies have suggested that patients do better when antibodies are used concurrently against two similar receptors. As Alitalo points out, time will tell whether targeting receptors will be as efficient as targeting their ligands. But he has good reasons to believe that his therapy can be at least as effective.

Lymphatic vessels enter the stage

The human genome encodes five VEGF proteins: VEGF-A-D, and placenta growth factor (PlGF); and three VEGFRs: VEGFR1-3. When Alitalo became interested in angiogenesis, only two VEGFs were known. They were VEGF-A, the most important family member (responsible for most angiogenic events), isolated by Harold Dvorak and Napoleone Ferrara, and PlGF, isolated by Graziella Persico, which was later shown to be responsible for angiogenesis and arteriogenesis. It was also known that these proteins bound to either VEGFR-1, or VEGFR-2, or both.

Alitalo's interest was fired after cloning a similar receptor that did not bind either of the known VEGFs. Alitalo started to search for the missing ligand and it wasn't long before he found it. "Together with Ulf Erikson from the Ludwig Institute for Cancer Biology in Stockholm, we cloned VEGF-B and Vladimir Joukov in my group cloned VEGF-C." By working mainly on VEGFs -B, -C and -D and the endothelial Tie1 receptor that he also discovered, Alitalo has since done a great deal to pin down the mechanisms that drive angiogenesis.

Alitalo explains, "VEGF-C and VEGF-D via VEGFR-3 regulate the growth of lymphatic vessels." Along with his collaborators, he has also shown that lymphangiogenesis plays a major role in causing tumours to metastasise. What's more, he showed that VEGF-C strongly enhances tumour metastasis when it is secreted by tumour or inflammatory cells. Alitalo's group has discovered inhibitors that can thwart two-thirds of dangerous lymphatic metastases in mice: a good strike-rate. These inhibitors are also now proceeding to clinical trials.

The function of VEGF-B has recently come under renewed scrutiny. To Alitalo's surprise, the evidence for this growth factor's role in angiogenesis has never been convincing, so his group over-expressed the protein in mice. When the transgenic mice were analysed, some angiogenesis was seen specifically in the heart. But, more importantly, the hearts were also larger and more muscular. They think that VEGF-B could also be involved in the metabolism of heart muscle cells.

Before establishing his group at the University of Helsinki, Alitalo spent time in the laboratories of Nobel Laureates Michael Bishop and Harold Varmus at the University of California in San Francisco. It was their work on oncogenes, successfully transferred to mice, which now allows the study of many types of cancer in a more natural setting. "Having trained in a medical field, I am very attracted to these *in vivo* models," says Alitalo. "We do a lot of high-throughput screening of pathways, looking at mechanisms, then proceeding to validation in *in vivo* models. It is very expensive but fascinating work."

Licensing provides income for the lab

Finding the money to fund such research brings its own challenges. In Finland, grants tend to be small. Over half of the money that Alitalo receives for his work comes from abroad, from large funding agencies. This funding model looks set to continue if the group wants to keep using high-throughput screens and *in vivo* treatment models. Twenty percent of the group's funding comes from the Finnish government, with the Centre of Excellence in Cancer Biology programme itself being funded by the Finnish Academy of Science.

Intellectual property is also a money spinner. The University of Helsinki, together with the Ludwig Institute for Cancer Research, has filed patents on various tools that are of potential benefit for the treatment of cancer patients. Some of these are licensed and Alitalo's group is involved in their preclinical development towards clinical trials. Licensing has already generated some income for the lab and Alitalo predicts that earnings could increase depending on clinical success.

Thanks to a well organised research programme, Alitalo's group has access to almost all the resources that are available to other leading medical science labs around the world. However, he craves the high density of renowned labs in research centres such as in Boston. To mimic this environment in Helsinki, programmes to concentrate labs into clusters have been set up and have already shown some success. Foreign groups are also being encouraged to settle in Finland, for example, with the call for a new Finnish Institute for Molecular Medicine, of which Alitalo is an associate member.

News about colon cancer

So, what are realistic goals for the treatment of cancer over the next twenty years? Alitalo explains that, "the beauty of the field is that one can design molecular, genomic and pathway diagnostics of tumours. In the coming years there will be less need to revert to general cytotoxic therapies to the extent that oncology currently has to." Alitalo foresees the analysis of the gene mutations behind a tumour as key to its successful treatment. This analysis, in combination with profiles of kinase activation, will lead to the selective targeting of signalling pathways specific to any given tumour, and an effective, personalised treatment programme.

What remains the most important unanswered question for Alitalo and his group? They would love to know whether tumours can really be halted at their primary stage. Alitalo explains, "metastasis is a great challenge, particularly the contribution of host cells such as bone marrow cells and also stem cells to the metastatic process". The group has recently discovered some of the progression mechanisms in colon cancer (Petrova *et al.*, *Cancer Cell* 13: 407-19) and in the future would like to focus on high-throughput screens for inhibitors of tumour progression. Stopping tumours from growing rather than eliminating them completely is how Alitalo sees the battle against cancer being won. He and his colleagues are sharpening their swords for the next fight.

The big C has a formidable opponent in Alitalo and his team.

William Teale