

Inhibiting angiogenesis and lymphangiogenesis – a powerful new treatment approach for cancer

Circadian Technology



VEGF Proteins

Circadian's technology is centred on two members of the vascular endothelial growth factor (VEGF) family of proteins, VEGF-C and VEGF-D, and their activation of the VEGF receptors. These proteins promote the key biological processes of blood vessel development (VEGFR-2) and lymphatic vessel development (VEGFR-3), known as angiogenesis and lymphangiogenesis respectively.

Angiogenesis and lymphangiogenesis

The growth of tumours is known to depend on the formation of new blood vessels to carry nutrients and oxygen to the new tissue. Targeting the process of angiogenesis has been

a major breakthrough in anti-cancer therapeutics – an approach that led to the commercialisation of Avastin®, a monoclonal antibody against VEGF-A.

While Avastin® has been demonstrated to be effective in fighting cancer, clinical results indicate that its effect in inhibiting angiogenesis is only partial. Hence there is a need for auxiliary or improved anti-angiogenesis agents.

In addition to regulating fluid levels in the body, the lymphatic system plays an important role in cancer progression. Lymph is filtered in the lymph nodes, trapping cancer cells that leave the site of a primary cancer.

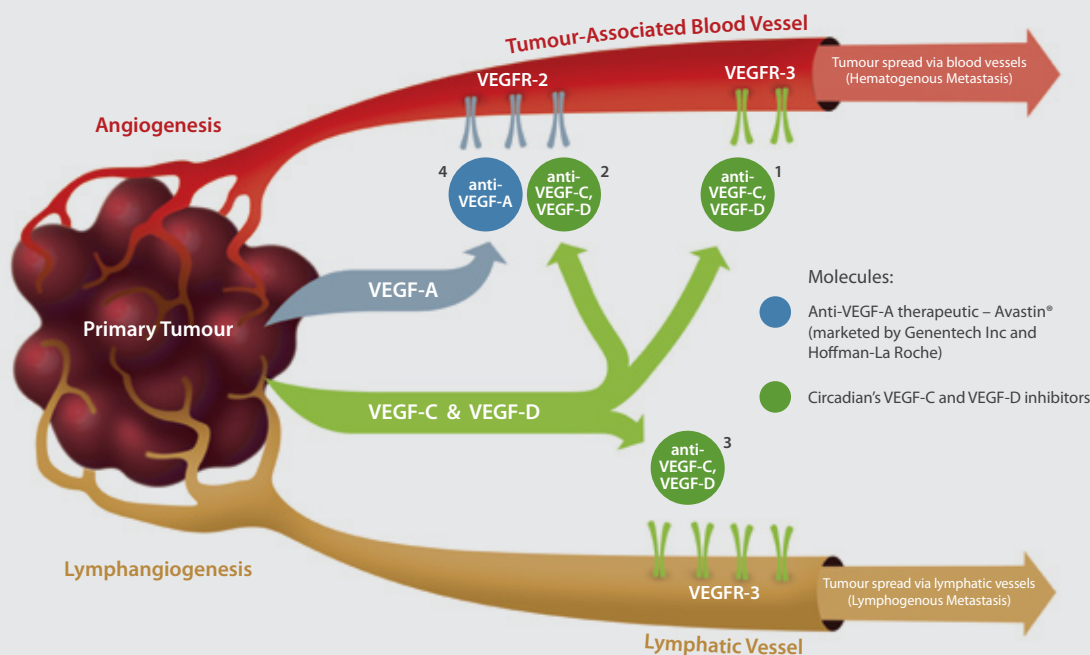
Recent evidence suggests that new lymphatic vessels formed by certain tumours (for example,

breast cancer) are a major means of spreading cancer to other sites in the body. Tumour spread is often the primary cause of cancer mortality and inhibiting lymphangiogenesis may therefore represent a powerful approach to preventing cancer spread.

About VEGF-C, VEGF-D and VEGFR-3

Closely related to VEGF-A (the target of Avastin®), proteins VEGF-C and VEGF-D bind to VEGF receptors promoting both angiogenesis and lymphangiogenesis.

VEGFR-3 is a receptor protein embedded in the plasma membrane of the cells that form lymphatic capillaries. Recently, work from the laboratory of the highly respected



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researcher Professor Kari Alitalo (University of Helsinki), has shown that VEGFR-3 plays an important role in cancer angiogenesis by guiding new blood vessels toward tumours. Studies by Circadian's scientists and its collaborators have shown that VEGFR-3 also plays an essential role in lymphatic vessel development.

These studies have led to a surge of interest in VEGF-C, VEGF-D and VEGFR-3 as potential new targets for anti-cancer therapy.

VEGFR-3 as an anti-cancer target

Several recent findings have further enhanced interest in VEGFR-3 as an important new drug target for cancer. These include:

- Over-expression of VEGFR-3 or its activators VEGF-C and VEGF-D correlates with poor prognosis in a variety of cancer types (as documented extensively in scientific publications)
- Circadian and its collaborators have shown that blocking VEGFR-3 or VEGF-C and VEGF-D inhibits tumour growth in various animal models.

In addition, the VEGFR-3 pathway has certain properties that make it especially attractive as a drug target:

- VEGFR-3 is expressed at the cell surface, so it is accessible to biotherapeutics such as antibodies or soluble receptor drugs
- The signalling pathway of VEGFR-3 is well understood, which facilitates the evaluation or ruling out of potential side-effects or toxicities.

Anti-cancer compounds

Inhibitors of VEGF-C, VEGF-D and VEGFR-3 block the activity of these proteins in a similar, but alternative, way to the multi-billion dollar drug Avastin®. As such, inhibitors of VEGF-C and VEGF-D have the potential to block blood vessel growth in tumours that are resistant, or have developed resistance, to anti-VEGF-A therapy. When used in combination with drugs like Avastin®, inhibitors of VEGF-C and VEGF-D may more effectively shut down angiogenesis.

Inhibitors of VEGF-C, VEGF-D and VEGFR-3 also have the potential to limit the spread of tumours – which is often the fatal event in cancer progression – through their effect on lymphangiogenesis. Anti-VEGF-A therapeutics have not shown efficacy in blocking the spread of tumours through the lymphatic system.

Intellectual property

Circadian owns the world's most extensive intellectual property portfolio related to VEGF-C, VEGF-D and VEGFR-3. These rights were originally licensed or assigned from a variety of parties including the Ludwig Institute for Cancer Research, the University of Helsinki and Human Genome Sciences. Circadian's rights to develop antibody-based drugs to these proteins are protected worldwide and as far into the future as 2025.

Other disease applications

While Circadian is focusing primarily upon cancer, VEGF technology also has applications in other diseases. Shutting down angiogenesis and/or lymphatic vessel growth is important in eye diseases including age-related macular degeneration and diabetic retinopathy. Circadian has licensed some of its intellectual property to other companies for exploration of these therapeutic opportunities.

Scientific collaboration



Circadian is working with some of the world's leading scientists to advance the field of angiogenesis/lymphangiogenesis and to develop new therapies for cancer. Pictured above are Circadian's collaborators and consultants Professors Kari Alitalo, University of Helsinki (centre) Marc Achen and Steven Stacker, Ludwig Institute, Melbourne (l,r).

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