

OFFICE OF TECHNOLOGY TRANSFER AND ENTERPRISE DEVELOPMENT

Methods & Antibodies to Regulate Angiogenesis

Summary

Vanderbilt scientists have discovered that the receptor tyrosine phosphatase DEP-1 plays a significant role in angiogenesis and that modulation of the DEP-1 receptor with certain agents can affect endothelial cell growth.

The research team has developed antibodies that bind to the ectodomain of a mammalian transmembrane

protein known as DEP-1 (for density enhanced protein) or CD148. CD148 (also named DEP-1/PTPn) is a receptor-like protein tyrosine phosphatase that is abundantly expressed in vascular endothelial cells, hematopoietic-cell lineages, duct epithelia of thyroid, mammary and gastrointestinal tissues.

Description

Angiogenesis, or the formation of new blood vessels, occurs under normal physiologic conditions in wound healing, fetal and embryonic development and formation of various tissues and blood vessels. Angiogenic stimulants cause endothelial cells to migrate and form sprouts off the parent blood vessel. Persistent, unregulated angiogenesis can occur in a variety of disease states, most notably in metastasis of a cancer. In this state, prevention and control of angiogenesis is desirable.

The findings show that mutant mice lacking catalytic activity of CD148 die at midgestation due to vascularization failure accompanied by increased endothelial-cell proliferation and vessel growth (1).

The specificity of these antibodies for the extracellular domain of the DEP-1/CD148 receptor protein lends itself to therapy that is highly selective for angiogenic biology and not other biological processes.

A monoclonal antibody has been made that binds specifically to the extracellular domain of DEP-1. Recent experiments show that the biologic effects of monovalent (Fab fragment) and bivalent (intact) antibody are different. The bivalent form of the antibody inhibits endothelial-cell growth and blocks angiogenesis in mouse cornea in vivo (2). These data demonstrate that the bivalent, but not monovalent, monoclonal antibody inhibits endothelial-cell growth and angiogenesis.

In addition, monovalent forms of the antibody may enhance endothelial cell growth and differentiation. This may be of use in stimulating new blood vessel growth, for instance, to improve blood flow to tissues (e.g. the heart) damaged by disease (heart attack, blood vessel blockage, etc.).



Potential Market Size

2007

Sales: \$12.6M

Oncology Segment: \$6.5M

Total Products: 16

2014 (est.)

Sales: \$34.4M

Oncology Segment: \$15.2M

Total Products: 37

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Advantages & Potential Uses

There are some significant advantages of CD148 mAb therapy, including 1) CD148 mAb does not cause endothelial damage and apoptosis, 2) it may suppress vascular leak, and 3) it may inhibit inflammation.

The specificity of these antibodies for the extracellular domain of the DEP-1/CD148 receptor protein lends itself to therapy that is highly selective for angiogenic biology and not other biological processes.

A reporter molecule could be attached to the antibody or fragment and used for in vivo imaging of tumors.

The monoclonal antibody and fragments thereof [e.g. Fab, F(ab')₂, scFv, etc.] specific for Dep-1 could also be labeled with toxins or isotopes and used to kill off new forming endothelial cells.

Potentially, a peptide or a peptide mimetic could be used to stimulate blood vessel growth in damaged tissue after a heart attack.

Intellectual Property Status

Patents issued in the U.S. 6,248,327 and 7,176,289

Patent issued in Australia No. 752649

Patents pending in Europe, Israel, Japan

Available for licensing and research partnering.

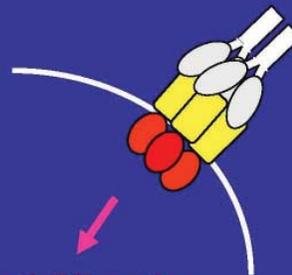
Selected Recent Publications

1. Takahashi et al, Mol Cell Biol. 2003; 23:1817-1831.
2. Takahashi et al, Blood 2006; 108: 1234-1242

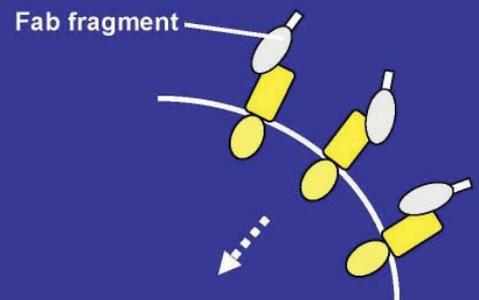
Bivalent, but not Monovalent, CD148mAb Inhibits Endothelial Cell Growth and Angiogenesis

Bivalent ()

Monovalent ()



Growth/Migration Arrest



Blood 108 (4): p1234-1242, 2006



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