L-11885

Potent VEGF antagonists as potential therapeutic agents

SUMMARY

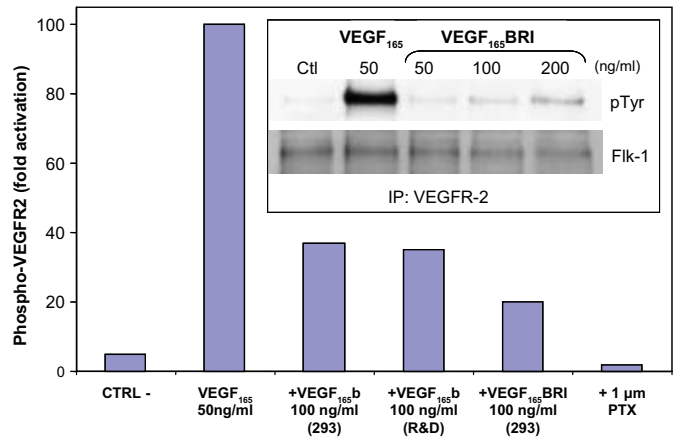
The growth of all tumor cells and metastasis is critically dependent on neovascularization via angiogenesis. Many pro-angiogenic factors drive tumor angiogenesis; however inhibition of vascular endothelial growth factor (VEGF) alone suffices to significantly impair angiogenesis and tumor growth. The present technology is a therapeutic targeting VEGF and its signaling through the VEGF receptor (VEGFR). Specifically, it provides non-natural mutants of a natural VEGF antagonist ($VEGF_{165}b$) that have the potential to compete with natural, pro-angiogenic ligands to inhibit VEGF signaling and subsequent pathological angiogenesis.

APPLICATIONS

- Targeted approach to inhibit VEGF activity.
- Potential therapeutic for use in various cancers, ophthalmic pathologies, and rheumatoid arthritis.

CONCEPT

VEGF and the signaling carried out through its receptor, VEGFR, plays a significant role in growth and development as well as in many pathological conditions such as cancer, and ophthalmic and inflammatory diseases. In oncology, VEGF's role in angiogenesis is critical for blood vessel formation facilitating tumor growth, invasion and metastasis. VEGF-A, the main regulator of angiogenesis, exists in at least four isoforms due to alternative splicing. One of these isoforms, $VEGF_{165}$, is a pro-angiogenic factor. A natural splice variant of this isoform ($VEGF_{165}b$) displays an inhibitory effect on angiogenesis. In many pathological conditions, this natural antagonist is down-regulated, which may cause increased angiogenesis and disease propagation. In the present technology, non-natural $VEGF_{165}b$ mutants that retain their anti-angiogenic properties were identified. These mutants are likely to have a positive safety profile due to minimal amino acid mutations from the natural antagonist and to offer greater potency. Therefore, these antagonists are potential candidates for the treatment of cancer and other VEGF-mediated pathologies.



The $VEGF_{165}$BRI mutant does not induce VEGFR2 activation (autophosphorylation - inset). However, it does antagonize $VEGF_{165}$-mediated (50 ng/ml) VEGFR2 activation at low dose and appears more potent than the natural splice variant antagonist $VEGF_{165}b$. As a control, the highly potent VEGFR2 kinase inhibitor PTX was used at 1 µM.

FEATURES AND BENEFITS

Numerous potential indications

The contribution of elevated VEGF expression and its signaling pathway has been associated to pathological angiogenesis in virtually all carcinomas studied as well as neovascular ophthalmic diseases such as age-related macular degeneration and retinopathy. VEGF may also play a role in inflammatory synovitis, the prototype of which is rheumatoid arthritis, where angiogenesis is considered an early step in disease progression.

Validated target

Anti-VEGF therapeutic agents have been well-validated in the clinic and on market as potent and specific inhibitors of VEGF signaling. The first marketed anti-VEGF biologic therapeutic for oncology, Genentech's monoclonal antibody Avastin, has been shown to be efficacious in three carcinomas to date and continues to be trialed for numerous additional indications.

Greater efficacy

Unlike the natural $VEGF_{165}b$ mutant, which has residual agonist activity, several of the non-natural mutants identified are likely to only exhibit antagonist activity. Consequently, they may demonstrate greater efficacy.

Good safety profile

The non-natural mutants differ from the natural $VEGF_{165}b$ isoform by only two amino acids, which is likely to offer a minimal immunogenic response and a good safety/ tolerability profile.

PROTECTION STATUS

Potent VEGF antagonists (NRC no. 11885).

CONTACTS

Yves Quenneville
Tel.: (514) 496-8507
Business Development Officer
E-mail: yves.quenneville@cnrc-nrc.gc.ca

Daniel Desmarteaux
Tel.: (514) 496-5300
Business Development Officer
E-mail: daniel.desmarteaux@cnrc-nrc.gc.ca

Dr. Yves Durocher
Tel.: (514) 496-6192
Animal Cell Technology Group
E-mail: yves.durocher@cnrc-nrc.gc.ca