

COMP:Angiopoietin-1

More Stable, Active and Potent

highlight

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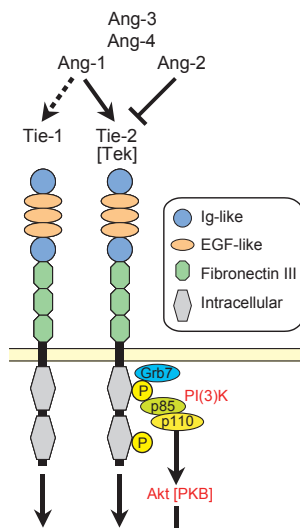
International Version

Angiopoietin-1 [Ang-1]

Angiopoietin-1 (Ang-1) is an important modulator of vascular homeostasis and angiogenesis. While vascular endothelial growth factor (VEGF), one of the best characterized pro-angiogenic molecules acts early during vessel formation, Ang-1 induces blood vessel remodelling and stabilization at a later stage.

In addition to Ang-1, the family of angiopoietins in human includes Ang-2 and Ang-4. It appears that Ang-3 is the mouse counterpart to human Ang-4. Although Ang-1 and Ang-2 both bind to receptor Tie-2 (for "tyrosine kinase with immunoglobulin and epidermal growth factor domains"), Ang-1 shows agonistic effects while Ang-2 exhibits antagonistic activity (see Fig. 1). The ratio of Ang-1, Ang-2 and VEGF to each other seem to regulate blood vessel formation and remodelling. This means Ang-1 completes VEGF induced angiogenesis during maturation and sta-

CONTINUED ON BACKCOVER



Survival, Sprouting, Stabilization, Permeability...

FIGURE 1: Schematic structure of the Tie receptors.

Product Highlight: COMP:Angiopoietin-1

NEW

COMP:Angiopoietin-1

To overcome the restrictions of economically produced Ang-1, a modified Ang-1 has been developed and called COMP:Ang-1 [6]. This recombinant protein contains a minimal coiled-coil domain, long enough for oligomerization but short enough to avoid problems of aggregation and insolubility (see Fig. 2). The variant is more potent than native Ang-1 in binding Tie-2 and its subsequent phosphorylation in primary cultured endothelial cells, enhancing angiogenesis *in vitro* and increasing adult angiogenesis *in vivo*. COMP:Ang-1 administered *in vivo* is mainly localized to microvascular endothelial cells of the intestinal villi and lung but not to microvascular endothelial cells of the liver [7]. In irradiated mice, *in vivo* administration of COMP:Ang-1 protects against radiation-induced apoptosis in microcapillary endothelial cells of the intestinal villi, prolongs survival, and promotes *in vivo* lymphatic angiogenesis in mouse cornea [7, 8]. Moreover, COMP:Ang-1 stimulates *in vitro* colony formation of lymphatic endothelial cells (LEC) and induces long-lasting vascular enlargement and increased tracheal blood flow [8, 9]. New results show that COMP:Ang-1 stimulates Tie-1 phosphorylation in endothelial cells with similar kinetics

COMP (rat):Angiopoietin-1, Soluble (human) (recombinant)

ALX-201-314-C010	10 µg
ALX-201-314-C050	50 µg
ALX-201-314-C500	500 µg

Produced in CHO cells. The fibrinogen-like domain (aa 284-498) of human Ang-1 (angiopoietin-1) is fused at the N-terminus to the coiled-coil domain of rat COMP (cartilage oligomeric matrix protein).

and angiopoietin dose dependence when compared with Tie-2 [10] (see Fig. 1).

LIT: [1] Tie receptors: new modulators of angiogenic and lymphangiogenic responses: N. Jones, et al; Nat. Rev. Mol. Cell Biol. 2, 257 (2001) • **[2]** Biomedical significance of endothelial cell specific growth factor, angiopoietin: G. Y. Koh, et al; Exp. Mol. Med. 34, 1 (2002) • **[3]** The enigmatic role of angiopoietin-1 in tumor angiogenesis: L. J. Metheny-Barlow & L. Y. Li; Cell Res. 13, 309 (2003) • **[4]** Angiopoietin-1 protects the adult vasculature against plasma leakage: G. Thurston, et al; Nat. Med. 6, 460 (2000) • **[5]** Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche: F. Arai, et al; Cell 118, 149 (2004) • **[6]** COMP-Ang1: a designed angiopoietin-1 variant with nonleaky angiogenic activity: C. H. Cho, et al; PNAS 101, 5547 (2004) • **[7]** Designed angiopoietin-1 variant, COMP-Ang1, protects against radiation-induced endothelial cell apoptosis: C. H. Cho, et al; PNAS 101, 5553 (2004) • **[8]** Angiopoietin-1 promotes LYVE-1-positive lymphatic vessel formation: T. Morisada, et al; Blood 105, 4649 (2005) • **[9]** Long-Term and Sustained COMP-Ang1 Induces Long-Lasting Vascular Enlargement and Enhanced Blood Flow: C. H. Cho, et al; Circ. Res. 97, 86 (2005) • **[10]** Multiple angiopoietin recombinant proteins activate the Tie1 receptor tyrosine kinase and promote its interaction with Tie2: P. Saharinen, et al; J. Cell Biol. 169, 239 (2005)

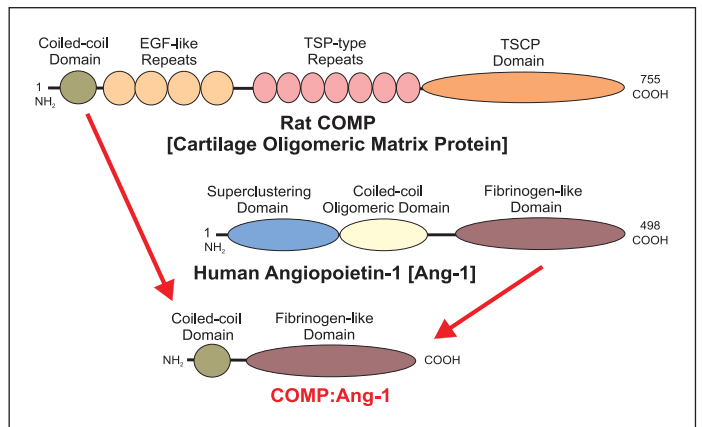


FIGURE 2: The fibrinogen-like domain (aa 284-498) of human Ang-1 (angiopoietin-1) is fused at the N-terminus to the coiled-coil domain of rat COMP (cartilage oligomeric matrix protein). For details of the cloning, see reference [6].

Angiotensin-1 [Ang-1]

bilization. Remarkably, Ang-1 shows a unique ability to oppose the effect of VEGF-induced vascular permeability [1-4]. Beside angiogenesis Ang-1 influences other biological processes, like the maintenance of the adult blood system by protecting hematopoietic stem cells (HSCs) [5].

The Ang-1 structure consists of a C-terminal fibrinogen-like domain that is responsible for receptor binding, a central coiled-coil domain that oligomerizes these fibrinogen-like domains, and a short N-terminal domain that

superclusters these oligomers into variably sized multimers (see Fig. 2). To achieve Tie-2 receptor oligomerization and activation, Ang-1 uses a modular and multimeric structure unlike that of any other known growth factor. However, the central coiled-coil domain and N-terminal superclustering domain responsible for the modular and multimeric structure of Ang-1 cause protein aggregation and insolubility which hinders large-scale production of recombinant Ang-1.

continued

Angiotensin-like Proteins

Six proteins have been identified containing a coiled-coil domain and a fibrinogen-like domain similar to those found in angiotensins, and designated angiotensin-like proteins (ANGPTL1-ANGPTL6). None of these proteins binds Tie-1 or Tie-2. ANGPTL3 and ANGPTL4 have been shown to regulate fat, lipid or glucose metabolic homeostasis. Recently, ANGPTL6 (also called AGF) has been identified as a novel angiogenic- and proliferation-promoting factor for skin cells which also harbors biological effects on nonvascular cells. As a hepatocyte-derived circulating factor it seems to counteract obesity and related insulin resistance. Several angiotensin-like proteins have been identified as potent stimulators of *ex vivo* expansion of hematopoietic stem cells (HSC).

LIT: Angiotensin-related growth factor (AGF) promotes epidermal proliferation, remodeling, and regeneration: Y. Oike, et al; PNAS 100, 9494 (2003) • Angiotensin-related growth factor (AGF) promotes angiogenesis: Y. Oike, et al; Blood 103, 3760 (2004) • Angiotensin-related growth factor antagonizes obesity and insulin resistance: Y. Oike, et al; Nat. Med. 11, 400 (2005) • Angiotensin-like proteins: potential new targets for metabolic syndrome therapy: Y. Oike, et al; Trends. Mol. Med. 11, 473 (2005) (Review) • Angiotensin-like proteins stimulate *ex vivo* expansion of hematopoietic stem cells: C. C. Zhang, et al; Nat. Med., in press (2006)

Angiotensins & Tie-1/-2 & Related Products

Angiotensin-1 & -2

NEW Angiotensin-1, Soluble (human) (rec.) (FLAG®)

ALX-201-313-C010	10 µg
ALX-201-313-C050	50 µg

Produced in CHO cells. Human Ang-1 (angiotensin-1) (aa 20-498) is fused at the N-terminus to a FLAG®-tag. **BIOLOGICAL ACTIVITY:** Induces the phosphorylation of Tie-2 in primary cultured human vascular endothelial cells.

NEW Angiotensin-2, Soluble (human) (rec.) (FLAG®)

ALX-201-315-C010	10 µg
ALX-201-315-C050	50 µg

Produced in CHO cells. Human Ang-2 (angiotensin-2) (aa 19-496) is fused at the N-terminus to a FLAG®-tag. **BIOLOGICAL ACTIVITY:** Induces the phosphorylation of Tie-2 in primary cultured human vascular endothelial cells.

Tie-1 & -2

Tie-1 (human):Fc (human), Soluble (rec.)

RLT-SFC-011-C020	20 µg
RLT-SFC-012-C100	100 µg

Disulfide-linked glycosylated homodimer produced in insect cells. Recombinant human soluble Tie-1 fused to the Fc portion of human IgG1.

LIT: Tie-1 and tie-2 define another class of putative receptor tyrosine kinase genes expressed in early embryonic vascular system: T.N. Sato, et al; PNAS 90, 9355 (1993) • Growth factors acting via endothelial cell-specific receptor tyrosine kinases: VEGFs, angiotensins, and ephrins in vascular development: N.W. Gale & G.D. Yancopoulos; Genes Dev. 13, 1055 (1999)

Tie-1 (mouse):Fc (human), Soluble (rec.)

RLT-SFC-031-C020	20 µg
RLT-SFC-032-C100	100 µg

Disulfide-linked glycosylated homodimer produced in insect cells. Recombinant human soluble Tie-2 fused to the Fc portion of human IgG1. **BIOLOGICAL ACTIVITY:** Binds recombinant human Ang-2 (angiotensin-2).

Tie-2 (mouse):Fc (human), Soluble (rec.)

RLT-SFC-033-C020	20 µg
RLT-SFC-034-C100	100 µg

Disulfide-linked glycosylated homodimer produced in CHO cells. Recombinant mouse soluble Tie-2 fused to the Fc portion of human IgG1.

Tie-2 (human):Fc (human), Soluble (rec.)

RLT-SFC-013-C020	20 µg
RLT-SFC-014-C100	100 µg

Disulfide-linked glycosylated homodimer produced in insect cells. Recombinant human soluble Tie-2 fused to the Fc portion of human IgG1. **BIOLOGICAL ACTIVITY:** When sTie-2 is immobilized at 4µg/ml (100µl/well) in functional ELISA assays, it binds recombinant human Ang-2 (angiotensin-2) within a linear range of 2-100ng/ml.

LIT: see RLT-SFC-011

Antibodies to Tie-1 & -2

MAb to Tie-1 (human) (8C9)

RLT-101-M46-C100	100 µg
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CLONE: 8C9. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human soluble extracellular Tie-1. **SPECIFICITY:** Recognizes native human Tie-1 on the surface of different human cell types. **APPLICATION:** ELISA, WB.

MAb to Tie-1 (human) (6F12)

RLT-101-M48-C100	100 µg
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CLONE: 6F12. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human soluble extracellular Tie-1. **SPECIFICITY:** Recognizes native human Tie-1 on the surface of different human cell types. **APPLICATION:** ELISA, WB.

MAb to Tie-2 (human) (2)

RLT-101-M50-C100	100 µg
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CLONE: 2. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human soluble Tie-2. **SPECIFICITY:** Recognizes human Tie-2. **APPLICATION:** ELISA, FC, WB.

MAb to Tie-2 (human) (9)

RLT-101-M52-C100	100 µg
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CLONE: 9. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human soluble Tie-2. **SPECIFICITY:** Recognizes human Tie-2. **APPLICATION:** ELISA, FC, WB.

MAb to Tie-2 (human) (16)

RLT-101-M54-C100	100 µg
RLT-101-MB54-C050	Biotin 50 µg

CLONE: 16. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human soluble Tie-2. **SPECIFICITY:** Recognizes human Tie-2. **APPLICATION:** ELISA, FC, WB.

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NEW ANGPTL1 (human) (rec.) (FLAG®)

ALX-201-345-C010	10 µg
ALX-201-345-C050	50 µg

Produced in HEK293 cells. Mature human ANGPTL1 (angiotensin-like protein 1) (aa 1-491) is fused at the C-terminus to a FLAG®-tag.

NEW MAb to ANGPTL3 (human) (1D10)

ALX-804-635-R050	50 µl
ALX-804-635-R100	100 µl

CLONE: 1D10. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human ANGPTL3 (angiotensin-like protein 3) (aa 243-460) produced in *E. coli*. **SPECIFICITY:** Recognizes human ANGPTL3. Detects bands of ~64kDa (full-length) and ~36kDa (cleaved ANGPTL3) by Western blot. **APPLICATION:** ELISA, WB.

NEW ANGPTL4, Soluble (human) (rec.) (FLAG®)

ALX-201-338-C010	10 µg
ALX-201-338-C050	50 µg

Produced in HEK293 cells. Mature human ANGPTL4 (angiotensin-like protein 4) (aa 26-406) is fused at the C-terminus to a FLAG®-tag.

NEW PAb to ANGPTL4 (rat)

ALX-210-360-C100	100 µg
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From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 80-94 (C⁸⁰QGPKGKDAPFKDSE⁹⁴) of mouse ANGPTL4 (angiotensin-like protein 4). **SPECIFICITY:** Recognizes rat ANGPTL4. Detects a band of ~50kDa by Western blot. **APPLICATION:** WB.

NEW ANGPTL6 [AGF], Soluble (human) (rec.) (FLAG®)

ALX-201-337-C010	10 µg
ALX-201-337-C050	50 µg

Produced in HEK293 cells. Mature human ANGPTL6 (angiotensin-like protein 6; AGF) (aa 21-470) is fused at the N-terminus to a FLAG®-tag.

NEW PAb to ANGPTL6 [AGF] (human)

ALX-210-430-C100	100 µg
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From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 114-130 (L¹¹⁴QHEAGPGAGP-GADLGA¹³⁰) of human ANGPTL6 (angiotensin-like protein 6; AGF). **SPECIFICITY:** Recognizes human ANGPTL6. **APPLICATION:** ELISA, WB.