

Title (en)
SOLUBLE DERIVATIVES OF ANTI-ANGIOGENIC PEPTIDES

Title (de)
LÖSLICHE DERIVATE VON ANTI-ANGIOGENISCHEN PEPTIDEN

Title (fr)
DERIVES DE POLYPEPTIDES

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Application
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Abstract (en)
[origin: WO0004052A2] It has been found that derivatives of angiogenesis inhibiting proteins may be prepared in which a negative feedback process can be enhanced for therapeutic purposes and which can be targeted to cell membranes and sites of active angiogenesis particularly those of the vascular endothelium. The invention provides a soluble derivative of a polypeptide capable of inhibiting angiogenesis, said derivative comprising a combination of heterologous membrane binding elements covalently associated with the polypeptide so that the derivative acquires affinity for the surface of the vascular endothelium particularly that of growing blood vessels. The soluble polypeptide may be selected from the non-catalytic regions of human plasminogen (within the N-terminal 560 residues of that protein); fragments thereof, particularly those generated by metalloprotease digestion of plasminogen; fragments of related proteins containing kringle domains such as hepatocyte growth factor or apolipoprotein (a), prothrombin, tissue-type plasminogen activator, urinary-type plasminogen activator and hybrids thereof with plasminogen sequences; mutants of the above kringle domains, those containing positively charged to neutral or negatively charged mutations at positions 20, 21, 78 and 79; fragments of collagen, particularly collagen XVIII; fragments of prolactin, the 16kDa N-terminal region of prolactin; neutralising antibodies against receptors for angiogenic mediators; antagonists of integrins involved in angiogenesis; and hybrids, derivatives or muteins thereof. Each membrane binding element with low membrane affinity may have a dissociation constant of 1 μ M-1mM, and the derivative may incorporate sufficient elements with low affinities for membrane components to result in a 0.01 - 10nM dissociation constant affinity for specific membranes.

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