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WO 2004/024089 A2

(54) Title: INHIBITION OR ACTIVATION OF ADAM9 AND ADAM15 FOR TREATMENT OF VASCULARIZATION-RELATED DISEASE AND WOUND HEALING

(57) Abstract: Inhibition of neovascularization is achieved by exposing a tissue susceptible to neovascularization to a therapeutic agent effective to inhibit ADAM 9 and/or ADAM 15. The therapeutic agent may be, for example, an antibody, a small molecule therapeutic, an antisense or RNAi therapeutic, or an agent for introducing targeted mutations in the genetic sequence for ADAM9 and/or ADAM 15. Thus, an individual suffering from a condition associated with pathological neovascularization is treated by administration of a therapeutic agent effective to inhibit a ADAM 9 or ADAM 15. Activation of ADAM9 or ADAM 15 can be used for promotion of neovascularization, for example to facilitate wound healing, perfusion or circulation. In this case, the therapeutic agent used is one which enhances the active amount of ADAM9 and/or ADAM15. Inhibition or activation of ADAM9 and/or ADAM15 in accordance with the methods of the invention provides an attractive alternative to targeting of other ADAM species, such as ADAM10, because neither ADAM9 nor ADAM15 appears to be essential for development or maintenance. Thus, side effects are minimised.

INHIBITION OR ACTIVATION OF ADAM9 AND ADAM15 FOR TREATMENT OF VASCULARIZATION-RELATED DISEASE AND WOUND HEALING

[0001] This application claims the benefit of US Provisional Application No. 60/409,858 filed September 11, 2002, which is incorporated herein by reference.

[0002] Background of the Invention

[0003] The present application relates to inhibition of vascularization via inhibition of metalloproteinase-disintegrin protein ADAM 9 or ADAM 15, and to the treatment of disease conditions by inhibition of disease-associated neovascularization. The present invention further related to activation of ADAM9 or ADAM15 for promotion of vascularization, for example to facilitate wound healing and for improvement of cardiac and brain perfusion and peripheral circulation.

[0004] ADAM 9 and ADAM 15 are members of the ADAM protein family, which combine disintegrin and metalloprotease functions. These proteins are also known as MDC9 and MDC15, respectively. The nucleic acid and peptide sequences for each protein are known in humans (NCBI NM_003816 and NM_003815,respectively, Seq. ID Nos 1-4), and other species (mouse, ADAM9: NM_007404; rat, ADAM15: NM_020308; mouse, ADAM15: NM_009614, Seq. ID Nos 5-7).

[0005] Members of the ADAM family are membrane-anchored proteins structurally related to snake venom disintegrins, and have been implicated in a variety of biologic processes involving cell-cell and cell-matrix interactions, including fertilization, muscle development, and neurogenesis. ADAM9 and ADAM15 each contains a metalloproteinase domain, a disintegrin domain and a cysteine-rich domain, as well as transmembrane and cytoplasmic domains.

[0006] Summary of the Invention

[0007] The present invention provides a method for inhibition of neovascularization comprising the step of exposing a tissue susceptible to neovascularization to a therapeutic agent effective to inhibit a ADAM 9 or ADAM15. The therapeutic agent may be, for example, an antibody, a small molecule therapeutic, an antisense or RNAi therapeutic, or an agent for introducing targeted mutations in the genetic sequence for ADAM9 and/or ADAM15. The tissue which is exposed may be a tissue in an individual to be treated, particularly a human individual. Thus a further aspect of the invention is a method for treatment of an individual suffering from a condition associated with pathological neovascularization by administration of a therapeutic agent effective to inhibit a ADAM 9 or ADAM15. This method may particularly be employed in the treatment of cancer patients to reduce tumor growth and tumor survival by inhibition of blood vessel formation, and in non-cancerous conditions related to neovascularization, including such as proliferative retinopathies.

[0008] The present invention further related to activation of ADAM9 or ADAM15 for promotion of neovascularization, for example to facilitate wound healing. In this case, the therapeutic agent used is one which enhances the active amount of ADAM9 and/or ADAM15.

[0009] Inhibition or activation of ADAM9 and/or ADAM15 in accordance with the methods of the invention provides an attractive alternative to targeting of other ADAM species, such as ADAM10, because neither ADAM9 nor ADAM15 appears to be essential for development or maintenance. Thus, side effects are minimized.

[0010] Brief Description of the Drawings

[0011] Fig. 1 shows structures of exemplary hydroxamic acid compounds useful as inhibitors in the invention.

[0012] Fig. 2 shows the results of testing using the ROP model in wildtype (wt), ADAM9 -/-, ADAM15 -/- and the double knockout (D -/-)

[0013] Fig. 3 shows tumor growth results in wildtype (wt), ADAM9 -/- and ADAM15 -/- mice.

[0014] Detailed Description of the Invention

[0015] In a first aspect, the present application relates to inhibition of pathological neovascularization via inhibition of metalloproteinase-disintegrin protein ADAM 9 or ADAM 15, or both. The term "ADAM9 and/or ADAM15" as used in the specification and claims of this application refers to these three alternatives.

[0016] As used in the specification and claims of this application, the term "pathological vascularization" refers to the formation of blood vessels associated with a disease condition, as distinguished from normal vascularization that is associated with growth, healing and the like. In particular, pathological vascularization is associated with cancers of various types, including without limitation colorectal, liver, renal, lung, breast, ovarian, prostate, brain, pancreas, stomach, and cervical cancers; some leukemias and lymphomas; and AIDS-related Kaposi's sarcoma. Pathological neovascularization is also associated with a variety of non-cancerous conditions, including without limitation Crohn's disease, diabetic retinopathy, retinopathy of prematurity, macular degeneration, prostate growth in benign prostate hypertrophy, psoriasis, and rheumatoid arthritis.

[0017] As used in the specification and claims of this application, the term "inhibition" refers to reduction in the rate or extent of formation of vascularization. It is not required that the inhibition be sufficient to completely eliminate pathological neovascularization, provided that neovascularization is inhibited to an extent that provides a therapeutic benefit.

[0018] As used in the specification and claims of this application, the term "enhance the active amount" refers to any increase in the amount of ADAM9 and/or ADAM15

providing stimulation of neovascularization, however, this increase is achieved. Thus, enhancement may occur by inducing additional expression of ADAM9 and/or ADAM15, or by delaying degradation of ADAM9 and/or ADAM15 to increase the number of protein molecules present, or by stimulating the enzyme present.

[0019] In accordance with the invention, inhibition of ADAM9 and/or ADAM15 is achieved by administration of a therapeutic agent effective to inhibit ADAM 9 and/or ADAM15. The therapeutic agent may be of any type effective to provide inhibition of ADAM9 and/or ADAM15, for example an antibody, a small molecule therapeutic, an antisense or RNAi therapeutic, or an agent for introducing targeted mutations in the genetic sequence for ADAM9 and/or ADAM15.

[0020] As used in the specification and claims of this application, an antibody therapeutic agent encompasses antibodies administered as such and antibodies generated *in situ*, for example as a result of administration and *in vivo* expression of DNA encoding an antigen or antigenic fragment effective to stimulate an immune response to a target antigen, and antibodies generated *in situ* by expression of a DNA sequence encoding a recombinant antibody. An antibody preparation may be a polyclonal or monoclonal preparation, or a recombinant antibody such as a single chain antibody (scFv) tolerated by the individual to whom the therapeutic agent is to be administered. For example, in the case of a human subject, a "humanized" antibody is appropriately employed. Techniques for creation of antibodies specific for a given target and for humanization are well known in the art, and therefore are not repeated here. Suitable targets for use in the development of antibody therapy include, without limitation, intact ADAM9, intact ADAM 15, portions of ADAM9 or ADAM15 derived from the extracellular portions of the protein, and in particular the protease and disintegrin domains of the extracellular portions of the protein.

[0021] Small molecule therapeutics useful in the invention are designed to interact with at least one of the active domains of ADAM9 and/or ADAM15 to provide inhibition. In general, such small molecule therapeutics are structurally related to the natural substrates of metalloprotease domain of the ADAM.

[0022] One particular class of small molecules which can be used as small molecule therapeutics in accordance with the invention are hydroxamic acid compounds. Hydroxamic compounds useful in the invention may be represented by the general formula

[0023] RCONHOH or R'N(OH)COOR".

[0024] In the compositions of the invention, the groups R, R' and R" are selected to provide inhibitory activity for ADAM9 and ADAM15. Exemplary materials of this type, and methods for identifying additional materials, are described in US Patent No. 6,465,468 which is incorporated herein by reference. Fig. 1 shows structures of exemplary hydroxamic acid compounds useful as inhibitors in the invention as described in Roghani et al. *J. Biol. Chem.* 274: 3531-3540 (1999).

[0025] Another small molecule approach to inhibition of ADAM9 and ADAM15 relies on the involvement of a cysteine-switch mechanism in regulation of metalloproteinase activity. (Van Wart et al., *Proc. Nat'l Acad. Sci (USA)* 87: 5578-5582 (1990); Grams et al., *FEBS Lett.* 335: 76-80 (1993)). The predicted cysteine-switch residue is a defined as an odd-numbered cysteine that is only present in the pro-domain of the metalloproteinase disintegrins that contain a catalytic site but not in those that lack a catalytic site. Peptides mimicking this switch can be used as inhibitors. In the case of ADAM9, the sequence for the human cysteine-switch inhibitor is PLKCGVSN (Seq. ID. No. 8) and the sequence for the murine cysteine-switch inhibitor is PLRCGVSN (Seq. ID. No. 9). Both were found to be effective at inhibiting murine ADAM9 in *in vitro* experiments. (Roghani et al., *supra.*)

[0026] Small molecule inhibitors of ADAM9 and/or ADAM15 can be targeted by conjugating the small molecule inhibitor to an antibody or fragment thereof. Conjugation methods are known in the art. These conjugated inhibitor-antibody species are then useful both in therapy and in monitoring the dosage of the inhibitors.

[0027] Antisense therapy depends on the ability of short sequences of DNA, generally from 8 to 30 bases in length, to inhibit a target protein species. In one model of antisense

activity, this inhibition occurs because of a sequence specific interaction of the DNA with mRNA leading to a reduction in protein expression. Other models for antisense activity have also been suggested, however, and it is not Applicants' intention to be bound by any specific mode of action. Antisense species for use in the method of the present invention are suitably derived from the coding sequence for ADAM9 and ADAM15 of the target organism. In the case of humans, these sequences are set forth in Seq ID Nos 1 and 3. The antisense sequence may be delivered in a lipid carrier or may be chemically modified to provide protection against nuclease attack. Antisense preparation techniques are known in the art, for example from US Patent No. 6,228,648 which is incorporated herein by reference and which describes antisense preparations targeted to ADAM10, and therefore are not repeated here.

[0028] RNA interference or "RNAi" is a term initially coined by Fire and co-workers to describe the observation that double-stranded RNA (dsRNA) can block gene expression when it is introduced into worms (Fire et al. (1998) Nature 391, 806-811, incorporated herein by reference). dsRNA directs gene-specific, post-transcriptional silencing in many organisms, including vertebrates, and has provided a new tool for studying gene function. RNAi involves mRNA degradation, but many of the biochemical mechanisms underlying this interference are unknown. The use of RNAi has been further described in Carthew et al. (2001) Current Opinions in Cell Biology 13, 244-248, and Elbashir et al. (2001) Nature 411, 494-498, both of which are incorporated herein by reference. US Patent Application 2002-0086356-A1, which is incorporated herein by reference, discloses a method for use in assessing where target sites might be located in a mRNA sequence, although this method is not the only approach to development of effective RNAi sequences. Specific RNAi sequences include without limitation:

aacagacctcacatctttctt Seq ID No. 10

aacagacctcacatctttcttctt Seq ID No. 11

aaggagccacgcaggcgggatt Seq. ID No. 12

and the complements thereof. The RNAi molecules may also be modified to protect against nuclease attack.

[0029] Inhibition of ADAM9 and/or ADAM15 may also be achieved through targeted mutation or gene therapy. In this case, mutations are introduced into the sequence of the ADAM9 or ADAM15 gene sequence at locations that disrupt the activity of the ADAM9 and/or ADAM15 gene product. Suitable targets include the active sites of the protease and the disintegrin portions of the protein, as well as the cleavage site associated with the transition from the originally expressed precursor ADAM to the active protein species.

[0030] For purposes of activating ADAM9 and/or ADAM15, for example for enhancing wound healing, to promote cardiac perfusion in patients with coronary artery disease to reduce the risk of heart attack, to improve brain perfusion in patients with atherosclerosis, and to improve peripheral circulation, small molecule species that enhance their activity, instead of inhibit it can be arrived at using methodologies similar to those used to test for inhibitors, for example using *in vitro* assays for protease activity, as outlined in Roghani et al, *supra.* Alternatively, small molecules that interfere with the maturation or degradation of ADAM9 or ADAM15 may be employed. For example, proteins that interact with the cytoplasmic domain of both ADAMs and regulate their maturation include the SH3 domain-containing proteins Endophilin I and SH3PX1, also known as sortin nexin 9 (SNX). Howard et al., *J. Biol. Chem.* 274: 31693-31699 (1999). Therefore the interaction between ADAMs 9 or 15 and these molecules, or other molecules that regulate their intracellular maturation or degradation, can be regulated by a drug, or by controlling the expression levels of these proteins. The screen or such a drug would be an increase or decrease in the levels of ADAM9 or ADAM15 on cells. Gene therapy to provide enhanced ADAM9 and/or ADAM15 is also a viable option, since the short duration of gene therapy that is frequently identified as a problem for gene therapy treatments is conducive to use in wound healing application where the need for treatment is of short duration as well. For gene therapy purposes, an expression vector compatible with the host such that protein is expressed from the vector in the host is used. The expression vector comprises a genetic sequence encoding ADAM9, ADAM15 or both, and a promoter which may, if desired, be inducible in response to a inducer molecule which can be applied locally in the wound region. Additional common elements, including suicide genes such as thymidine kinase, or marker genes to allow detection of expression may also be included.

[0031] The therapeutic agent is administered to a subject in need of treatment in a therapeutically effective amount. Appropriate amounts will depend on the specific therapeutic agent, the route of administration, the cause of the pathological vascularization, and a balancing of the degree of inhibition or activation required with toxicity and side effects. Appropriate therapeutic amounts are routinely determined in accordance with standard protocols, and do not require anything more than routine experimentation.

[0032] The route of administration will depend on the nature of the condition being treated and the form of the therapeutic agent, and may include without limitation intravenous, subcutaneous, transdermal, intraperitoneal, parenteral injections and topical applications.

[0033] The invention will now be further described with reference to the following, non-limiting example.

[0034] ADAM9 -/-, ADAM15 -/- and ADAM9 -/- ADAM15 -/- knockout mice were prepared and their response to relative hypoxia was compared to wildtype mice in a retinopathy of prematurity (ROP) model. In this model, which was developed to study retinopathy in premature infants and diabetic retinopathy, hypoxia leads to neovascularization of the retina, ultimately resulting in loss of vision. In the ROP model, 7 day old mice and their mothers are placed in a chamber with an oxygen concentration of 75% for 5 days, and then returned to normal air. The resulting drop in oxygen levels triggers a relative hypoxia. This leads to an increase in the production of VEGF, which is turn results in neovascularization. The parameter measured in the ROP model is an increase in the number of retinal endothelial cells after 5 days in normoxic air. Eyes are collected in 4% paraformaldehyde, embedded, sectioned and stained with periodic acid/Schiff reagent and hematoxilin. The number of retinal vascular cell nuclei on the vitreal side of the inner limiting membrane is counted on several 6 μm sections per eye by a blinded observer.

[0035] Fig. 2 shows the results of this test using the ROP model in wildtype (wt), ADAM9 -/-, ADAM15 -/- and the double knockout (D -/-). There are a significant decrease

in the amount of neovascularization in mice lacking ADAM15, but an actual increase in mice lacking ADAM9. This observation originally suggested that ADAM9 and ADAM15 acted in contrary manners, providing the potential for modulation of neovascularization either upward or downward. It was therefore surprising to find that growth of melanoma cells was reduced in both ADAM9 -/- and ADAM15 -/- mice, as compared to wildtype mice. Fig. 3 shows the results of this study, in which B16F10 melanoma tumors were grown in mice and the size of the tumor measured.

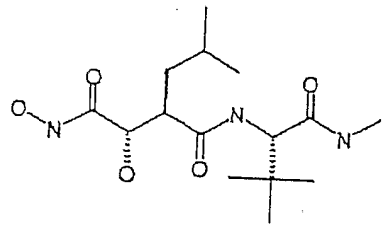
What is claimed is:

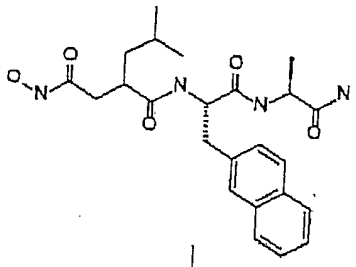
1. A method for inhibition of neovascularization comprising the step of exposing a tissue susceptible to neovascularization to a therapeutic agent effective to inhibit a ADAM 9 or ADAM15.

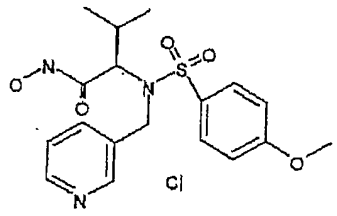
2. The method of claim 1, wherein the therapeutic agent is a small molecule therapeutic.

3. The method of claim 2, wherein the therapeutic agent is a hydroxamic acid derivative.

4. The method of claim 3, wherein the therapeutic agent is selected from the group consisting of







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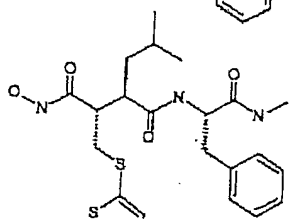


5. The method of claim 1, wherein the therapeutic agent is an antibody, antisense or RNAi.

6. A method for treatment of a pathological condition associated with pathological neovascularization in an individual suffering from the pathological condition comprising the

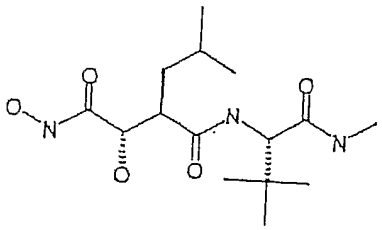
step of inhibiting neovascularization by administering to the individual a therapeutically effective amount of a therapeutic agent effective to inhibit a ADAM 9 or ADAM15.

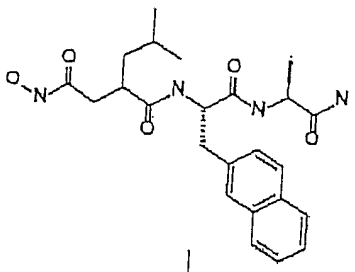
7. The method of claim 6, wherein the individual is human.

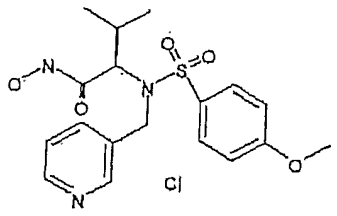
8. The method of claim 7, wherein the therapeutic agent is a small molecule therapeutic.

9. The method of claim 8, wherein the therapeutic agent is a hydroxamic acid derivative.

10. The method of claim 9, wherein the therapeutic agent is selected from the group consisting of







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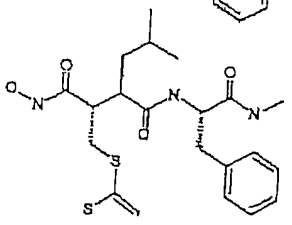
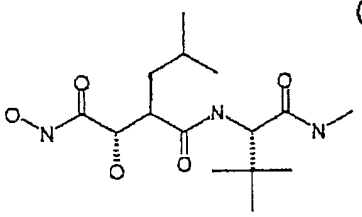


11. The method of claim 7, wherein the therapeutic agent is an antibody, antisense or RNAi.

12. A method for promoting neovascularization comprising the step of exposing a tissue in need of neovascularization to a therapeutic agent effective to enhance the amount of active ADAM 9 or ADAM15 or both in the tissue, thereby promoting neovascularization.

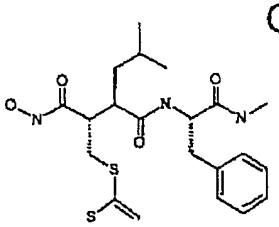
13. The method of claim 12, wherein the tissue is a wound site, and neovascularization is needed to promote healing.

Chiral



marimastat

Chiral



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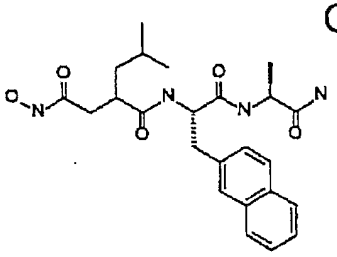

TAPI

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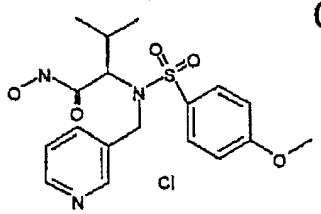
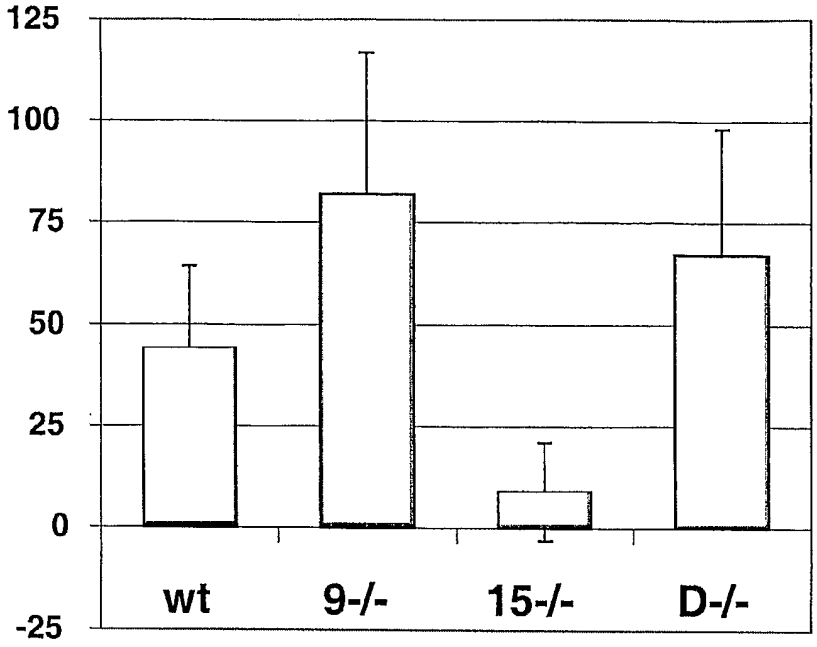


CGS 27023

FIG. 1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wt
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15-/-
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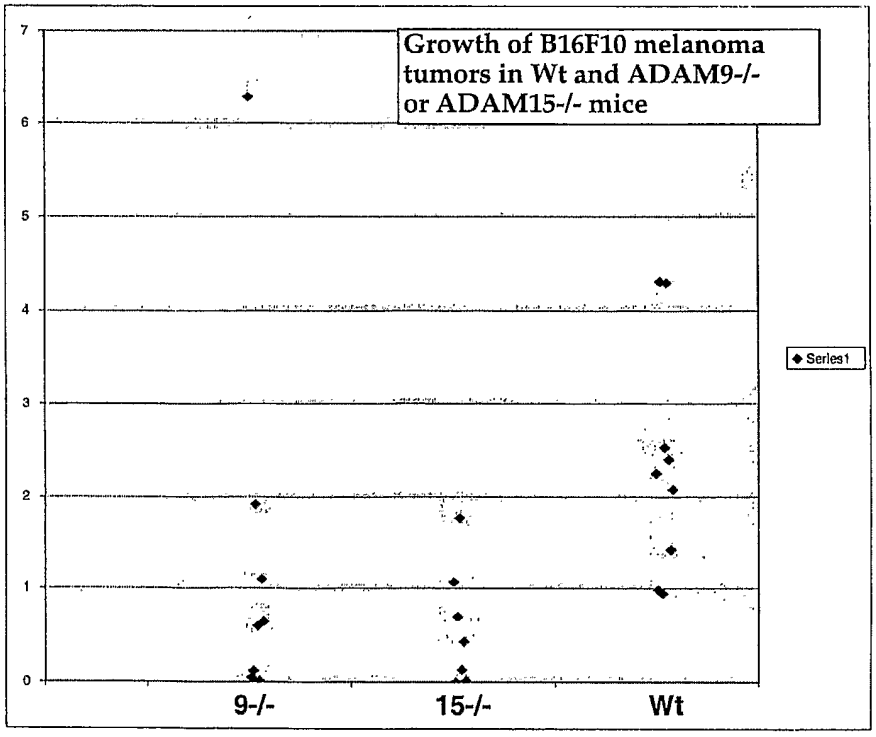
FIG. 2


Growth of B16F10 melanoma tumors in Wt and ADAM9-/- or ADAM15-/- mice
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Wt
Series1

FIG. 3

SEQUENCE LISTING

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University of Mannheim/Heidelberg
Justus-Liebig-Universität Giessen
Blobel, Carl
Horiuchi, Keisuke
Weskamp, Gisela
Preissner, Klaus
Hammes, Hans-Peter

<120> INHIBITION OR ACTIVATION OF ADAM9 AND ADAM15 FOR TREATMENT OF VASCULARIZATION-RELATED DISEASE AND WOUND HEALING

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Trp Arg Leu Thr Arg Glu Arg Arg Glu Ala Pro Arg Pro Tyr Ser Lys
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Gln Val Ser Tyr Val Ile Gln Ala Glu Gly Lys Glu His Ile Ile His
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Leu Glu Arg Asn Lys Asp Leu Leu Pro Glu Asp Phe Val Val Tyr Thr
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Tyr Asn Lys Glu Gly Thr Leu Ile Thr Asp His Pro Asn Ile Gln Asn
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His Cys His Tyr Arg Gly Tyr Val Glu Gly Val His Asn Ser Ser Ile
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Val Ser Asn Lys Asp Ile Glu Lys Glu Thr Ala Lys Asp Glu Glu Glu
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Glu Pro Pro Ser Met Thr Gln Leu Leu Arg Arg Arg Arg Ala Val Leu
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Pro Gln Thr Arg Tyr Val Glu Leu Phe Ile Val Val Asp Lys Glu Arg
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Tyr Asp Met Met Gly Arg Asn Gln Thr Ala Val Arg Glu Glu Met Ile
225                 230                 235                 240

Leu Leu Ala Asn Tyr Leu Asp Ser Met Tyr Ile Met Leu Asn Ile Arg
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            260                 265                 270

Ile Val Gly Gly Ala Gly Asp Val Leu Gly Asn Phe Val Gln Trp Arg
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Glu Lys Phe Leu Ile Thr Arg Arg Arg His Asp Ser Ala Gln Leu Val
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Val Cys Ser Arg Ser His Ala Gly Gly Ile Asn Val Phe Gly Gln Ile
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Thr Val Glu Thr Phe Ala Ser Ile Val Ala His Glu Leu Gly His Asn
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Leu Gly Met Asn His Asp Asp Gly Arg Asp Cys Ser Cys Gly Ala Lys
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Ser Cys Ile Met Asn Ser Gly Ala Ser Gly Ser Arg Asn Phe Ser Ser
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Cys Ser Ala Glu Asp Phe Glu Lys Leu Thr Leu Asn Lys Gly Gly Asn
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Pro Lys Glu Cys Glu Leu Asp Pro Cys Cys Glu Gly Ser Thr Cys Lys
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Ser Lys Gly Asp Arg Phe Gly Asn Cys Gly Phe Ser Gly Asn Glu Tyr
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Lys Lys Cys Ala Thr Gly Asn Ala Leu Cys Gly Lys Leu Gln Cys Glu
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Asn Val Gln Glu Ile Pro Val Phe Gly Ile Val Pro Ala Ile Ile Gln
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Thr Pro Ser Arg Gly Thr Lys Cys Trp Gly Val Asp Phe Gln Leu Gly
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Ser Asp Val Pro Asp Pro Gly Met Val Asn Glu Gly Thr Lys Cys Gly
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Ala Gly Lys Ile Cys Arg Asn Phe Gln Cys Val Asp Ala Ser Val Leu
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Asn Tyr Asp Cys Asp Val Gln Lys Lys Cys His Gly His Gly Val Cys
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Asn Ser Asn Lys Asn Cys His Cys Glu Asn Gly Trp Ala Pro Pro Asn
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Cys Glu Thr Lys Gly Tyr Gly Gly Ser Val Asp Ser Gly Pro Thr Tyr
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Asn Glu Met Asn Thr Ala Leu Arg Asp Gly Leu Leu Val Phe Phe Phe
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Asp Gln Leu Trp Arg Ser Tyr Phe Arg Lys Lys Arg Ser Gln Thr Tyr
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Glu Ser Asp Gly Lys Asn Gln Ala Asn Pro Ser Arg Gln Pro Gly Ser
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Val Pro Arg His Val Ser Pro Val Thr Pro Pro Arg Glu Val Pro Ile
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Gln Phe Pro Ser Arg Pro Pro Pro Pro Gln Pro Lys Val Ser Ser Gln
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Ser Leu Thr

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Gln Ala Glu Ser Glu Lys Ala Pro Arg Glu Pro Leu Glu Pro Gln Val
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Leu Gln Asp Asp Leu Pro Ile Ser Leu Lys Lys Val Leu Gln Thr Ser
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Leu Pro Glu Pro Leu Arg Ile Lys Leu Glu Leu Asp Gly Asp Ser His
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Ile Leu Glu Leu Leu Gln Asn Arg Glu Leu Val Pro Gly Arg Pro Thr
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Leu Val Trp Tyr Gln Pro Asp Gly Thr Arg Val Val Ser Glu Gly His
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Thr Leu Glu Asn Cys Cys Tyr Gln Gly Arg Val Arg Gly Tyr Ala Gly
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Ser Trp Val Ser Ile Cys Thr Cys Ser Gly Leu Arg Gly Leu Val Val
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Leu Thr Pro Glu Arg Ser Tyr Thr Leu Glu Gln Gly Pro Gly Asp Leu
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Gln Gly Pro Pro Ile Ile Ser Arg Ile Gln Asp Leu His Leu Pro Gly
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His Thr Cys Ala Leu Ser Trp Arg Glu Ser Val His Thr Gln Thr Pro
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Pro Glu His Pro Leu Gly Gln Arg His Ile Arg Arg Arg Arg Asp Val
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Val Thr Glu Thr Lys Thr Val Glu Leu Val Ile Val Ala Asp His Ser
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Glu Ala Gln Lys Tyr Arg Asp Phe Gln His Leu Leu Asn Arg Thr Leu
225                 230                 235                 240

Glu Val Ala Leu Leu Leu Asp Thr Phe Phe Arg Pro Leu Asn Val Arg
                245                 250                 255

Val Ala Leu Val Gly Leu Glu Ala Trp Thr Gln Arg Asp Leu Val Glu
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Ile Ser Pro Asn Pro Ala Val Thr Leu Glu Asn Phe Leu His Trp Arg
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Arg Ala His Leu Leu Pro Arg Leu Pro His Asp Ser Ala Gln Leu Val
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Thr Gly Thr Ser Phe Ser Gly Pro Thr Val Gly Met Ala Ile Gln Asn
305                 310                 315                 320

Ser Ile Cys Ser Pro Asp Phe Ser Gly Gly Val Asn Met Asp His Ser
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Thr Ser Ile Leu Gly Val Ala Ser Ser Ile Ala His Glu Leu Gly His
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Ser Leu Gly Leu Asp His Asp Leu Pro Gly Asn Ser Cys Pro Cys Pro
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Gly Pro Ala Pro Ala Lys Thr Cys Ile Met Glu Ala Ser Thr Asp Phe
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Leu Pro Gly Leu Asn Phe Ser Asn Cys Ser Arg Arg Ala Leu Glu Lys
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Leu Pro Pro Met Ala Ala Phe Cys Gly Asn Met Phe Val Glu Pro Gly
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Glu Gln Cys Asp Cys Gly Phe Leu Asp Asp Cys Val Asp Pro Cys Cys
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Asp Ser Leu Thr Cys Gln Leu Arg Pro Gly Ala Gln Cys Ala Ser Asp
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Ser Ser Gln Cys Pro Pro Asp Val Ser Leu Gly Asp Gly Glu Pro Cys
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Ala Gly Gly Gln Ala Val Cys Met His Gly Arg Cys Ala Ser Tyr Ala
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Gln Gln Cys Gln Ser Leu Trp Gly Pro Gly Ala Gln Pro Ala Ala Pro
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Leu Cys Leu Gln Thr Ala Asn Thr Arg Gly Asn Ala Phe Gly Ser Cys
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Gly Arg Asn Pro Ser Gly Ser Tyr Val Ser Cys Thr Pro Arg Asp Ala
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Ile Cys Gly Gln Leu Gln Cys Gln Thr Gly Arg Thr Gln Pro Leu Leu
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Gly Ser Ile Arg Asp Leu Leu Trp Glu Thr Ile Asp Val Asn Gly Thr
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Glu Leu Asn Cys Ser Trp Val His Leu Asp Leu Gly Ser Asp Val Ala
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Gln Pro Leu Leu Thr Leu Pro Gly Thr Ala Cys Gly Pro Gly Leu Val
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Cys Ile Asp His Arg Cys Gln Arg Val Asp Leu Leu Gly Ala Gln Glu
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Cys Arg Ser Lys Cys His Gly His Gly Val Cys Asp Ser Asn Arg His
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Cys Tyr Cys Glu Glu Gly Trp Ala Pro Pro Asp Cys Thr Thr Gln Leu
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Lys Ala Thr Ser Ser Leu Thr Thr Gly Leu Leu Leu Ser Leu Leu Val
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Leu Leu Val Leu Val Met Leu Gly Ala Gly Tyr Trp Tyr Arg Ala Arg
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Leu His Gln Arg Leu Cys Gln Leu Lys Gly Pro Thr Cys Gln Tyr Arg
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Ala Ala Gln Ser Gly Pro Ser Glu Arg Pro Gly Pro Pro Gln Arg Ala
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Pro Arg Lys Pro Leu Pro Ala Asp Pro Gln Gly Arg Cys Pro Ser Gly
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Asp Leu Pro Gly Pro Gly Ala Gly Ile Pro Pro Leu Val Val Pro Ser
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