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Enablement of Method Claims Encompassing the Immunotherapy of Cancer

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Enablement Determination

Method claims that encompass the treatment of cancer are evaluated on a case-by-case basis in accordance with the 1st paragraph of 35 U.S.C. 112.

In particular, do the claims enable one skilled in the art to predictably "use" the invention in the absence of undue experimentation?

Wands Factors Analysis.

Common Classes/subclasses

424/184.1

Subject matter involving bodily treatment with an antigen, an epitope, or another immunospecific immunoeffector.

424/130.1

Subject matter involving bodily treatment with an immunoglobulin, an antiserum, an antibody, or an antibody fragment.

424/93.1

Subject matter involving bodily treatment with a whole and living micro-organism, cell, or virus or its spore form.

436/64

Processes or compositions which chemically detect the presence of cancer.

435/7.23

Subject matter in which a measurement or test utilizes tumor or cancerous cells in an antibody binding, specific binding protein or other specific ligand-receptor binding test or assay.

Example I

Claim 1. A method of inhibiting angiogenesis in a patient comprising administering the polypeptide of SEQ ID NO:1 wherein said patient has a disease or disorder associated with increased cellular proliferation.

35 USC 112, 1st Paragraph (Enablement)

The specification shall contain a written description ... of the manner and process of making and using the invention, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same….” (35 USC 112, 1st paragraph)

MPEP 2164.01(a) Undue Experimentation Factors (*In re Wands*):

(1) The breadth of the claims
(2) The nature of the invention
(3) The state of the prior art
(4) The level of one of ordinary skill
(5) The level of predictability in the art
(6) The amount of direction provided by the inventor
(7) The existence of working examples
(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Example I, Scenario 1

A method of inhibiting angiogenesis in a patient comprising administering the polypeptide of SEQ ID NO:1 wherein said patient has a disease or disorder associated with increased cellular proliferation.

1. The specification teaches that diseases or disorders associated with increased cellular proliferation include, but are not limited to, cancer.
2. The specification teaches that SEQ ID NO:1 is one of many novel polypeptides obtained by homology screening to known secreted proteins.
3. A working example discloses an *in vitro* model of angiogenesis depicting the inability of HUVEC cells to form capillary-like structures or tubules in the presence of SEQ ID NO:1 versus control.

Example I, Scenario 1

A method of inhibiting angiogenesis in a patient comprising administering the polypeptide of SEQ ID NO:1 wherein said patient has a disease or disorder associated with increased cellular proliferation.

Breadth of the claims: The scope of the claimed invention includes the treatment of cancer and other diseases marked by cell proliferation that require neovascularization for growth.

Nature of the Invention: Biological therapy of cancer with an anti-angiogenic polypeptide.

State of the Prior Art: Protein database searches of SEQ ID NO:1 revealed no substantial homology to well-known or well-characterized proteins.

Example I, Scenario 1

A method of inhibiting angiogenesis in a patient comprising administering the polypeptide of SEQ ID NO:1 wherein said patient has a disease or disorder associated with increased cellular proliferation.

State of the Prior Art: The HUVEC assay

Bagley *et al.* (Cancer Res. 2003 Sep; 63(18):5866-73.) teach that investigators have formally tied circulating endothelial *precursor* cells to the development of the tumor vasculature. In contrast, HUVECs are normal, mature endothelial cells which may not be representative of the tumor endothelium.

Staton *et al.* (Int J Exp Pathol. 2004 Oct85(5):233-48) teach that endothelial cells that are stimulated to proliferate in cultured assays undergo changes in activation state, karyotype, expression of cell surface antigens and growth properties. This presents a significant limitation to the use of such cells to model *in vivo* angiogenesis because "endothelial cells are normally quiescent in adult blood vessels."

Example I, Scenario 1

State of the Prior Art: *In vitro* angiogenic assays

Auerbach *et al.* (Cancer Metastasis Rev. 2000;19(1-2):167-72) teach that with regard to *in vitro* assays that seek to model the angiogenic process, most can be exceedingly useful in screening for specific functions (*e.g.,* mitogen for vascular endothelial cells; inhibition of cytokine secretion; reduction in cell motility). However, these assays frequently do not translate into effects on angiogenesis *in vivo* because of the complex nature of *in vivo* angiogenesis. "In all instances, *in vitro* screens can help identify optimal compounds or likely concentrations for efficacy, but they must be followed by *in vivo* studies."

Example I, Scenario 1

Level of Predictability/State of the Art: While biological therapy has emerged as an important fourth modality for the treatment of cancer, it is still in its infancy. (DeVita *et al.* Cancer. Principles & Practices of Oncology, Lippincott Williams & Wilkins. 6th Edition. 2001. Chapter 18, page 307).

Even when going from animals to human clinical trials, *in vivo* therapy with anti-angiogenic compounds can present a degree of unpredictability. For example, Clamp *et al.* (British Journal of Cancer, 2005;93:967-972) reported that three phase I trials using recombinant human endostatin in a total of 61 patients with advanced metastatic disease showed no formal disease responses. Additionally, the reference highlights the difficulty of establishing a biologically effective dose along with the rapid induction of an immune response against the anti-angiogenic peptide.

Example I, Scenario 1-Conclusion

1. The examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *See* MPEP 2164.02. Based on the state of the prior art, it is unclear whether or not HUVEC cells are involved in the angiogenic process. This raises the level of unpredictability.

2. The predictability or lack thereof in the art refers to "the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention." *See* MPEP 2164.03. Based on the lack of predictability of the HUVEC assay coupled with the infancy of biological therapy, one skilled in the art would not extrapolate the results of the assay to the biological therapy of cancer via inhibition of angiogenesis.

Example I, Scenario 1-Conclusion

In view of the state of the art of HUVEC assays and the biological therapy of cancer, coupled with the breadth of the claims, the lack of specific guidance and the working examples in the specification, it would not be predictable for one of skill in the art to use the claimed method as contemplated in the disclosure. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Means to Obviate the Enablement Rejection

Has a reasonable basis to question the enablement been established? *See* MPEP 2164.04

Applicants may submit arguments and/or evidence that the disclosure as filed is enabled. *See* MPEP 2164.05

To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing.

Example I, Scenario 2

A method of inhibiting angiogenesis in a patient comprising administering the polypeptide of SEQ ID NO:1 wherein said patient has a disease or disorder associated with increased cellular proliferation.

1. The specification teaches that diseases or disorders associated with increased cellular proliferation include, but are not limited to, cancer.
2. The specification asserts that SEQ ID NO:1 is a novel member of a family of well-known anti-angiogenic polypeptides because it shares a common repeat domain known to be critical for anti-angiogenic activity.
3. A working example discloses that SEQ ID NO:1 inhibits angiogenesis in a rat aortic ring assay (RARA).

Example I, Scenario 2

A method of inhibiting angiogenesis in a patient comprising administering the polypeptide of SEQ ID NO:1 wherein said patient has a disease or disorder associated with increased cellular proliferation.

Breadth of the claims: The scope of the claimed invention includes the treatment of cancer and other diseases marked by cell proliferation that require neovascularization for growth.

Nature of the Invention: Inclusive of biological therapy of cancer with an anti-angiogenic polypeptide.

State of the Prior Art: A prior art search of SEQ ID NO:1 reveals substantial homology to a class of known anti-angiogenic polypeptides. Further, a review of the literature discloses that several of these polypeptides in the prior art have demonstrated anti-cancer activity in nude mice carrying a variety of different tumor xenografts.

Example I, Scenario 2

A method of inhibiting angiogenesis in a patient comprising administering the polypeptide of SEQ ID NO:1 wherein said patient has a disease or disorder associated with increased cellular proliferation.

Predictability in the art:

"The aortic ring organ-culture system has disadvantages that are hard to overcome. Quantitation is exceedingly difficult, growth requirements differ between the explant and the cell outgrowth, serum-free cultures are only marginally successful, and, although the cell outgrowth may be of microvascular origin, the model as a whole is only mildly representative of the microvascular organ environment encountered during angiogenic reactions induced by tumors or inflammatory mediators." (Auerbach *et al.* Cancer Metastasis Rev. 2000; 19(1-2):167-72)

Example I, Scenario 2

A method of inhibiting angiogenesis in a patient comprising administering the polypeptide of SEQ ID NO:1 wherein said patient has a disease or disorder associated with increased cellular proliferation.

Predictability in the art:

However, the state of the art of assessing angiogenesis also teaches that the rat aortic ring assay (RARA) is "widely used" and considered by many to come close to "simulating the *in vivo* situation". (Auerbach *et al.* Clin.Chem. 2003 Jan.;49(1):32-40).

Example I, Scenario 2-Conclusion

Existence of Working Examples:

1. Although the RARA assay is only mildly representative of the microvascular milieu, one skilled in the art would acknowledge that this assay reasonably demonstrates that SEQ ID NO:1 effectively functions as an anti-angiogenic agent.
2. Moreover, based on sequence similarity and structural conservation of the repeat domain common to the broader class, one skilled in the art would reasonably predict that SEQ ID NO:1 would inhibit angiogenesis in a broad class of tumors that require neovascularization for growth.
3. Example I, Scenario 2 is enabled.

Example II

Claim 1. A method for treating pancreatic cancer in a patient comprising administering to said patient an antibody that binds to the amino acid sequence of SEQ ID NO:1.

Example II, Scenario 1

1. The specification teaches that SEQ ID NO:1 is a novel polypeptide found to be predominantly expressed on the surface of pancreatic tissue.
2. A working example revealed that a well known growth factor cytokine bound specifically to the polypeptide of SEQ ID NO:1.
3. The specification discusses (prophetically) that monoclonal antibodies to SEQ ID NO:1 could be generated so that when administered to human patients with pancreatic cancer, the antibody blocks the growth-factor cytokine from binding to cancerous pancreatic cells.

A method for treating pancreatic cancer in a patient comprising administering to said patient an antibody that binds to the amino acid sequence of SEQ ID NO:1.

Breadth of the Claims

The claims are specifically drawn to treating pancreatic cancer in a patient. Based on the teachings of the specification, one of ordinary skill in the art could reasonably interpret a "patient" to include a human.

USPTO personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997).

The State of the Prior Art

It is well known in the oncology literature that pancreatic cancer is one of the most difficult cancers to treat. For example, Spinelli *et al.* (JOP, 2006 Sep 10;7(5):486-91) teaches that "pancreatic cancer remains one of the most severe neoplastic diseases since it is rarely detected in an early stage." The authors further note that in the past decades, the prognosis of pancreatic cancer - mainly correlated with tumor stage - has not been significantly improved by *any* procedure.

Compared to the conventional modalities of surgery, radiation, and chemotherapy, antibody-directed therapies are still in their infancy. Further, there are many factors, including physical barriers, that can contribute to a high degree of unpredictability in the delivery of antibodies to tumors. (Flessner *et al.*, Clin Cancer Res. 2005 Apr 15:11 (8):3117-25) (Jain, R., Cancer Research, 1990 Feb;50:814s-819s)

The Existence of Working Examples/Guidance

- The specification and the state of the prior art fail to disclose a biological nexus between the binding of antibodies to SEQ ID NO:1 on pancreatic tissue with regression of pancreatic cancer cell growth.

- While the natural ligand may be a well-known growth factor, the specification fails to deduce any concomitant biological activity associated with its binding to the polypeptide of SEQ ID NO:1 in pancreatic tissue. Thus, there is no evidence that the growth factor is antagonistic or agonistic in normal or pancreatic cancer cells.

The Existence of Working Examples/Guidance

- The specification does not teach a working example of treating pancreatic cancer patients with *any* antibodies.
- The specification does not disclose the inhibition of ligand binding to SEQ ID NO:1 on pancreatic cells.
- There is no evidence that the polypeptide of SEQ ID NO:1 is differentially expressed in pancreatic cancer as compared to normal pancreatic tissue.

Predictability of the Art and the Enablement Requirement

In cases involving unpredictable factors, such as predicting the effects of chemical reactions or physiological activity, more information may be required. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); *see also* MPEP 2164.03

Example II, Scenario 1- Conclusion

- The specification lacks the necessary guidance and objective evidence to enable one of skill in the art to treat pancreatic cancer as claimed.
- The state of the art and the nature of the invention are inherently unpredictable and complex. Compounded by the lack of working examples, one of ordinary skill in the art would not have a reasonable expectation of success.
- Lack of working examples can be given added weight in cases involving an unpredictable and undeveloped art such as the treatment of pancreatic cancer with antibodies.

In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that it would require undue experimentation to successfully practice the invention as claimed.

Example II, Scenario 2

A method of treating pancreatic cancer in a patient comprising administering to said patient an antibody that binds to the amino acid sequence of SEQ ID NO:1.

1. Through microarray analysis, the specification identifies a cDNA that is more abundantly expressed in pancreatic tumor cell lines compared to normal pancreatic cells.
2. Comparative sequence analysis of the encoded polypeptide (SEQ ID NO:1) revealed 75% amino acid identity to a known growth factor receptor.
3. Following generation of a monoclonal antibody specific for SEQ ID NO:1, Western blotting of primary pancreatic tumor tissue revealed dense staining patterns of SEQ ID NO:1 compared to little or no staining in normal pancreatic tissue.
4. A working example discloses tumor regression in nude mice bearing pancreatic tumor xenografts following administration of a monoclonal antibody specific to SEQ ID NO:1

Example II, Scenario 2- Conclusion

Because the claims are limited to the treatment of pancreatic cancer and because there is a working example that is reasonably correlative to the scope of the claimed subject matter, one skilled in the art would conclude that the claimed invention was enabled.

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