**Biotechnology**

Online Homework Set

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Advanced Patent Prosecution Workshop 2021:

*Claim Drafting & Amendment Writing*

**BIOTECHNOLOGY**

**Claim Drafting**

# Homework Problem #1

January 15, 2009

The following application was filed by Attorney Incompetent naming Dr. N. Inventor and Dr. A. Discoverer. Both are employed by PDQgen, a small biotech company in LaJolla, California It was assigned application no. 12/345,678.

**You are to prepare a new set of claims and provide arguments for overcoming the rejections.**

A NEW PROTEIN (VIP) USEFUL FOR TREATING  
PDQ RETROVIRUS INFECTIONS

BACKGROUND OF THE INVENTION

According to the World Health Organization, there are currently 600,000 cases of the recently recognized IRS (Immuno-Ravaging Syndrome) worldwide. It is estimated that by 2000, the number of cases will have increased to 11 million. IRS is caused by a retrovirus designated PDQ. The PDQ virus (like HIV) exerts a profound cytopathic effect on CD4 helper/inducer T-cells, which devastates the immune system. PDQ virus also results in hepatotoxicity, renal insufficiency, neurologic deterioration and eventual death of the infected individual [Smart et al., Morbidity Weekly, August 13, 1995].

Researchers in the field of viral therapeutics have actively pursued agents effective against the PDQ retrovirus. The complete DNA sequence of the PDQ virus has been described by G.N. Sequencer, The Journal, January, 1995, pp. 99-150. The Sequencer article also discloses that the PDQ virus requires at least three viral proteins for replication: a Reverse Transcriptase (RT), a protease, and a transactivator protein (MTV).

Anglin et al. have shown that the cell line XOX (ATCC Accession No. 100,000) is resistant to PDQ virus infection (Anglin et al., The Journal, June, 1994, pp. 500-550). Anglin et al. collected supernatant from this cell line, concentrated it 10 times, and demonstrated that when the concentrated supernatant was used to treat a culture of XBX cells infected with the PDQ virus, partial protection was obtained. Anglin et al. postulated that the XOX cell line produced a polypeptide that inhibited the PDQ virus, probably by inhibiting the MTV transactivator protein. Anglin et al., however, were unable to purify the putative protective protein to homogeneity, probably because it was present in such low concentrations in the supernatant isolated from the cell line.

The PDQ-infected XBX cell assay used by Anglin to test the antiviral effect of their supernatant has also been shown to be indicative of an in vivo anti-viral effect in PDP-infected cynomolgus monkeys. PDP is the monkey analog to PDQ, which only infects humans. Like PDQ, the PDP virus is known to be transactivated by MTV. Jones et al., The Journal, June, 1995, pp. 440-494, in fact, have demonstrated that three compounds shown to inhibit the PDQ virus in XBX cells also adduce an anti-viral effect in PDP-infected monkeys.

OUR INVENTION

We treated the cell line XOX with UV light plus nitrosoguanidine (as detailed by Dingbatt et al., The Journal, May 1988, pp. 85-105) to stimulate mutagenesis. We surprisingly found that certain mutants produced increased anti-viral activity, as discussed further below.

We cultured XOX cells obtained from The Cell Line Company in RPMI 1640 medium + 10% heat inactivated fetal bovine serum + 50 µg/ml of gentamycin. A T-75 flask containing 100 ml of medium and approximately 106 XOX cells per ml was treated for 10 seconds with UV light from a 300 watt Model XYZ UV lamp (which has an emission spectrum with a peak at 3600 at a distance of 10 cm. The UV-treated cells were pelleted and resuspended in 100 ml of a 1 mM solution of nitrosoguanidine in phosphate buffered saline (PBS) and allowed to stand for 10 minutes. The resultant cells were again pelleted and washed three times with PBS. Treated cells were plated out at approximately 10 cells/ml, 100 µl/well in 96-well culture plates. After 96 hours of culture in RPMI 1640 medium containing 1 mg/ml BSA (37ºC and 5% CO2), the supernatants were removed for assay and fresh medium was added to the cells. Supernatants from 1000 viable clones were screened in the XBX cell assay as detailed below to identify those producing the highest levels of anti-viral activity.

XBX cells used in the viral inhibition assay were obtained from the ATCC (ATCC accession No. 110,000). The XBX assay procedures were first described by I.M. Smart, The Journal, March, 1991, pp. 95-115. All reagents used were purchased from Fisher Scientific unless otherwise stated.

XBX cells were pre-infected with PDQ virus 24 hours prior to the addition of the test materials. Cells were plated at 2 x 103/ml, 100 µl/well in 96 well plates with 1:5 serial dilutions of the test material in RPMI 1640 medium + 10% fetal bovine serum. Cells were cultured in a 37ºC, 5% CO2 incubator for 96 hours in the presence of the test material and parallel concentrations of a control protein, ovalbumin. Twenty-four wells received no test material or control. N=12 wells per treatment group were used for all doses. At the end of the culture period, cells were counted for viability by trypan blue exclusion (a standard technique in the art).

The supernatants from the 1000 XOX mutant clones were used as the test material in the above procedure. Untreated XBX cells were all dead (0% inhibition), as well as all cells on the plate receiving the parallel doses of the control protein, ovalbumin. The supernatants from five XOX mutant clones showed significantly greater antiviral activity in the XBX screening assay than the original XOX cell line supernatant. One mutant (designated 632E), producing the supernatant with the highest anti-viral activity (1000 times the starting XOX cell line supernatant), was selected for further Investigation. A cell line sub-cloned from the initial 632E clone was thereafter designated XOXE.

We prepared cDNA from this cell line in order to clone the DNA encoding the anti-PDQ viral activity using techniques established in the art. Basically, we extracted the total mRNA from 109 XOXE cells by the procedure described in Berger et al., Biochemistry, 18, 5143-5149 [1979]. The mRNA was enriched using an oligo-dT column. The double stranded cDNAs were constructed using oligo-dT primer-initiated reverse transcription (Verma , I., Biochem. Biophys. Acta, Vol. 473, pgs. 1-38 [1977]) to make first the complement of each mRNA sequence, and then using Klenow fragment to initiate second strand-synthesis (Land, H., et al., Nucleic Acids Res., 9:2251-2266 [1981]). Subsequently, the cDNAs were cloned by litigation into pcD expression vectors [commercially available from the XXX Co.) developed by Okayama and Berg ("functional cloning") as disclosed in Mol. Cell. Biol., Vol. 2, pgs. 161-170 (1982); and Vol. 3, pgs. 280-289 (1983). The pcD expression vector contains the SV40 early promoter, late splicing junction, and the replication origin. This vector permits expression screening of cDNA inserts in COS 7 monkey cells. Accordingly, recombinant vectors containing the cDNAs were transfected into COS 7 cells using DEAE-Dextran. The resulting transfected cells were then monitored for expression of antiviral activity.

Because the COS 7 cells secrete the antiviral activity into the culture medium, the supernatants from the transfected cells after incubation for four days were assayed for activity in the XBX screening assay described above. Positive pools were further divided until we identified a single cDNA clone (pcD-999) which gave antiviral activity in the XBX screening assay.

The cDNA from this positive clone was excised from the vector DNA and sequenced by automated sequence analysis using an ABC Systems Sequencer (Model #ABC2.1) using dye terminator chemistry and found to have the following DNA and deduced amino acid sequences in relevant part (the middle part of the sequence has been fully characterized, but is omitted here for purposes of brevity)(SEQ ID NO:1, DNA and SEQ ID NO:2, amino acid):

ATG AGC ACT GAA ATC GAG ATC CGG TTG GTG 30

Met Ser Thr Glu Ile Glu Ile Arg Leu Val

-10 -5

GTC AGA TCA CCC CGG CGA ACC TCT AGT GAC 60

Val Arg Ser Pro Arg Thr Ser Asp Cys Ser

1 5 10

AAG TCT GTA GCC CAT GTT GTA GCA AAC CCT

Lys Ser Val Ala His Val Ala Asn Pro Pro

15 20

CCA GTC GAG GTC AGA TCA GTA GCC CAT. . . . . . . . . .

Gln Ala Glu . . Val Arg Ser. . . Val Ala His. . . . . . . . . . .

29. . . . . . . . . .

GAC TTT ACC GAG TCT GGG CAG GCC TAC TTG 240

Asp Phe Thr Glu Ser Gly Gln Ala Tyr Leu

71 80

GGG ATC ATT GCC CTG TGA 258

Gly Ile Ala Leu Stop

85

The numbers below the amino acid sequence indicate the position in the putative mature or signal protein. The protein having this amino acid sequence was designated the "viral inhibitory protein" (VIP).

Other nucleic acids encoding VIP were subsequently identified by hybridization to the complement of the VIP cDNA sequence in pcD-999 under high stringency conditions (i.e. hybridization to filter-bound DNA in 0.5M NaHPO4 at 65˚C and washing in 0.1X SSC / 0.1% SDS at 68˚C) or moderate stringency conditions (i.e. washing in 0.2X SSC / 0.1% SDS at 42˚C) (Ausubel, F.M. et al., 1998 Current Protocols in Molecular Biology, Vol. 1, Green Publishing Associates Inc. and John Wiley & Sons Inc., New York).

The COS 7 cells harboring the pcD-999 vector were cultured for eight days in serum-free Eagle's minimum essential medium to allow expression and secretion of larger amounts of VIP. The crude supernatant was found to have 1 mg/ml of protein per ml and produced 50% inhibition of virally-induced mortality in the XBX cell assay. After centrifugation, the protein mixture was purified using preparative HPLC to isolate a fraction which provided the maximum anti-viral activity in the XBX screening assay. When analyzed by SDS-PAGE, this fraction resolved into two bands. The bands were eluted and further characterized. It appears that each band contained one protein. Therefore, the HPLC fraction contained two proteins, VIP1 and VIP2. The amino acid sequence was determined for VIP1 and VIP2 as well as likely DNA sequences encoding VIP1 and VIP2 respectively and are shown below:

VIP1 (SEQ ID NO:3, DNA and SEQ ID NO:4, protein):

GTC AGA TCA CCC CGG CGA ACC TCT AGT GAC 60

Val Arg Ser Pro Arg Thr Ser Asp Ser Asp

1 5 10

AAG TCT GTA GCC CAT GTT GTA GCA AAC CCT

Lys Ser Val Ala His Val Ala Asn Pro Ser

15 20

CCA GTC GAG GTC AGA TCA GTA GCC CAT. . . . . . . . . .

Gln Ala Glu . . Val Arg Ser. . . Val Ala His

VIP2 (SEQ ID NO:5, DNA and SEQ ID NO:6, protein):

Val Ala His. . . . . . . . . . .

29. . . . . . . . . .

GAC TTT ACC GAG TCT GGG CAG GCC TAC TTG 240

Asp Phe Thr Glu Ser Gly Gln Ala Tyr Leu

71 80

GGG ATC ATT GCC CTG TGA 258

Gly Ile Gly Ile Ala Leu Stop

Purified VIP1 and VIP2, as well as a preparation of VIP1 and VIP2 were tested in the XBX screening assay described above. Each assay employed approximately 1000 XBX cells infected with 100 focus forming units (ffu) of the PDQ virus. The VIP proteins were employed in this assay in eight (1:5) serial dilutions starting at 25 µg/ml down to 1.6 ng/ml. Twenty-five micrograms per ml of the VIP1/VIP2 preparation conferred 95% inhibition of virally induced mortality; 5 µg/ml, 1 µg/ml, 200 ng/ml, 40 ng/ml and 8 ng/ml produced 86%, 70%, 50%, 32%, and 11% inhibition, respectively. Concentrations of 1.6 ng/ml and 0.32 ng/ml were both essentially ineffective in inhibiting virally induced mortality. Purified VIP thus has a specific activity of about 5000 IC50 units/mg of protein. Forty micrograms per ml of purified VIP1 conferred 95% inhibition of virally induced mortality; 5 µg/ml, 1 µg/ml, 200 ng/ml, 40 ng/ml and 8 ng/ml produced 50%, 25%, 10% inhibition, respectively. A concentration of 10 ng/ml was essentially ineffective in inhibiting virally induced mortality. Purified VIP1 thus has a specific activity of about 3500 IC50 units/mg of protein. VIP2 was essentially ineffective in inhibiting virally induced mortality. However, it was found to bind to VIP1.

We also ligated the VIP cDNA sequence, described above, into a pBR322 vector for cloning and expression from the B-lac promoter in E. coli. Cultured E. coli harboring such recombinants were found to express VIP1 and VIP2 proteins which could be purified by HPLC.

VIP1 or VIP1/VIP2 is thus believed to be an agent suitable for treating a patient infected with a PDQ retrovirus. In this treatment, VIP1 or VIP1/VIP2 would be administered in an anti-virally effective amount to the patient. A preferred dosage range is from 0.01 to 10 mg/kg body weight per day, more preferably from 0.1 to 4 mg/kg. A suitable dosage is one that achieves a blood level of 0.01 to 10 µM, preferably from 0.1 to 5 µm. VIP can be administered in various dosage forms, including tablets, capsules, rectal suppositories and compositions for topical, buccal, intravenous, parenteral, etc., administration. Conventional adjuvants for these modes of administration can also be employed in such pharmaceutical compositions.

We have now produced muteins of VIP1 by conventional site-specific oligonucleotide-directed mutagenesis using the methodology disclosed in Zoller and Smith, Methods in Enzymology, Vol. 100, pgs. 468-500 (1983). Three such muteins were made -- mutein No. 1 with a single amino acid change (Pro or Leu at position 20 of the mature VIP1), mutein No. 2 with a single amino acid change (Glu or Tyr at position 23), and mutein 3 with two amino acid changes (Pro or Leu at position 20 and Ala or Leu at position 78).

We also used conventional site-specific mutagenesis to make two truncated versions of VIP by inserting a stop codon 5-codons and 10-codons, respectively, from the C-terminus of the above DNA sequence. These two truncated versions of VIP1 were thus missing 5 and 10 amino acid residues, respectively, from the C-terminus.

Lastly, we prepared primers which were complementary to codons 6-10 and 11-15 of the mature VIP1 DNA sequence shown in DISCLOSURE No. 1 but also included an ATG preceding the complementary sequence. These primers were used in a conventional polymerase chain reaction (PCR) system (Mullis et al., Nobel Lecture, 1992) to produce two truncated DNA sequences encoding mature VIP1 but omitting the codons for the first 5 and 10 amino acid residues, respectively. Thus, the two truncated DNA sequences when placed in an appropriate vector produced truncated versions of mature VIP1 having a initial MET amino acid residue but missing the first 5 and 10 N-terminal amino acids of mature VIP1, respectively.

The four truncated versions of the VIP DNA all produced proteins having a specific activity of about 4000 IC50 units/mg of protein. Muteins Nos. 1 and 2 above produced a specific activity of about 4500 IC50 units/mg of protein, while mutein No. 3 above produced a specific activity of about 5500 IC50 units/mg of protein.

The truncated versions and muteins can be used in the same manner as that described above for VIP1 itself. Other truncated versions and muteins of VIP1 can also be prepared by the same techniques. These truncated versions and muteins preferably have a specific activity of greater than about 3000 IC50 units/mg protein, more preferably greater than about 3500 IC50 units/mg protein.

WHAT IS CLAIMED IS:

1. A DNA for making a protein having the anti-viral activity of VIP1.

2. A DNA for making a protein having the VIP1 binding activity of VIP2.

3. A protein having the antiviral activity of VIP1.

4. A protein having the VIP1 binding activity of VIP2.

5. A method of making a protein having the anti-viral activity of VIP1 comprising

making a vector including the DNA of claim 1, wherein the DNA is capable of being expressed by a host containing the vector; incorporating the vector into the host; and maintaining the vector-containing host under conditions suitable for expression of the DNA to produce the protein.

6. A method of making a protein having the VIP1 binding activity of VIP2 comprising

making a vector including the DNA of claim 2, wherein the DNA is capable of being expressed by a host containing the vector; incorporating the vector into the host; and maintaining the vector-containing host under conditions suitable for expression of the DNA to produce the protein.

7. A pharmaceutical composition comprising an anti-virally effective amount of the protein of claim 3 or the biological equivalent thereof.

8. A pharmaceutical composition comprising an anti-virally effective amount of a protein having the antiviral activity of VIP1protein and a protein having the VIP1 binding activity of VIP2 or the biological equivalent thereof.

9. A method for treating a patient infected with a virus comprising administering an anti-viral effective amount of the pharmaceutical composition of claim 7 or 8 or the biological equivalent thereof.

10. A mutant of cell line XOX, which mutant produces increased amounts of VIP.

11. DNA for producing a truncated VIP, wherein the codons for up to 10 amino acid residues from the N-terminus and/or up to 10 amino acid residues from the C-terminus are omitted.

12. VIP wherein up to 10 amino acid residues from the N-terminus and/or up to 10 amino acid residues from the C-terminus are omitted.

**Office Action and Client Correspondence**

June 1, 2012: An Office Action is issued with respect to this application

July 2, 2012: You receive a desperate telephone call from Drs. Inventor and Discoverer asking you to take over the prosecution of the application. To impress the new clients, your firm instructs you to prepare and file a response to Office Action before the deadline of September 1, 2010. Prepare such a response.

THE OFFICE ACTION (June 1, 2012)

35 U.S.C. 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title."

Claims 1 and 2 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. VIP and DNA encoding VIP are naturally occurring components of XOX cells.

Claims 2, 4, 6 and 8 are rejected under 35 U.S.C. §101 because the claimed invention is not supported by a well-established utility. There is no disclosed or real world utility associated with the claimed protein or protein encoded by the claimed DNA sequence. Further experimentation is necessary to attribute a utility to the claimed protein. See *Brenner v. Manson,* 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966).

Claims 2, 4, 6 and 8 have also been rejected under 35 U.S.C. §112, first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, 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 and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-9 and 11-12 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Applicants claim the VIP1 and VIP2 proteins, DNA encoding the VIP1 and VIP2 proteins, methods of making VIP1 and VIP2, and a method of treatment of viral infection comprising administering VIP1 and VIP1/VIP2.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (United States v. Teletronics Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is needed is not based upon a single factor, but rather a conclusion reached by weighing many factors. The Board and Court in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988), respectively, described the standard of undue experimentation as a standard of reasonableness and set forth the various factors to be considered in the determination of enablement for an invention. These factors include the following:

1) Unpredictability of the prior art. The prior art in treatment of retroviral infection is extremely unpredictable. This unpredictability is manifested at the level of delivery of the therapeutic agent, stability, susceptability to proteases, host immunological responses, toxicity, etc.

2) State of the art. The state of the art in treatment of retroviral infection is very poorly developed. The clinical efficacy has not been unambiguously demonstrated for any method of treatment of PDQ retroviral infection.

3) Amount of guidance presented by applicants. Applicants present no working examples of the use of the claimed invention. Applicants present examples of in vitro data, however, the relevance of this data to relevant disease conditions in vivo is unclear. Essentially, applicants' specification is an invitation for the skilled artisan to practice trial and error experimentation in order to try to use the claimed invention.

4) Scope of the invention. Claim 9 reads broadly on a method of treating any viral infection.

5) Number of working examples. Applicants present no working examples of the use of the claimed invention.

6) Level of skill in the art. The level of skill in the retroviral infection art is high; however, as noted by the cited prior art, those of skill in the art have encountered significant unsolved problems associated with practicing the use of protein therapeutics for treatment of PDQ retroviral infection.

7) Nature of the invention. The nature of the invention involves the complex and unpredictable field of treatment of retroviral infection.

Given the analysis of the above factors which the Courts have indicated are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to practice undue and excessive experimentation in order to use the claimed invention.

It is noted that the protein and DNA claims are included in this rejection because the only disclosed use of the claimed proteins is for treatment of PDQ infection, and the only disclosed use of the DNA is for production of the protein. Since applicants have not taught the skilled artisan how to practice the method of treatment, it must be considered that applicants have not taught the skilled artisan how to use the claimed protein and DNA.

Claims 1-6 and 11-12 are further rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification in another respect. Claims 1, 2, 5, 6, and 11 cover all possible DNA sequences that will encode any protein having the anti-viral activity of VIP and methods of using such sequences to produce such proteins, as well as the proteins themselves. Claims 3, 4, 5, 6 and 11 in effect encompass any protein having the anti-viral activity of VIP and the use of such proteins. The specification discloses only 9 proteins (VIP1, 3 muteins and 4 truncated versions and VIP2) and the DNA sequences encoding these proteins. This disclosure is inadequate to support the breadth of claims 1-6 and 11-12.

Claims 1, 2, 5, 6 and 11 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims rejected for inadequate written description are drawn to DNA for making a protein having VIP1 or VIP2 activity, a method of making a protein using said DNA, DNA for producing truncated VIP1, and mutant DNA for producing a VIP1 mutein.

The claimed DNA is described in generic terms in the specification. To determine whether there is correspondence between the generic invention of the claims and the written description, it is necessary to determine whether the description conveys to one skilled in the relevant art that applicant was in possession of the claimed genus at the time the application was filed. To this end, it is appropriate to inquire whether a number of species representative of the genus are described in complete structural terms or, alternatively, with reference to other identifying characteristics, e.g., partial structure, chemical properties, functional properties, etc. What constitutes a representative number of species for any given genus depends in part on whether the level of skill in the art, the teachings in the disclosure, or teachings in the prior art establish predictability as to the structural properties characteristic of the genus. The specification provides adequate written description for one DNA by disclosure of its nucleotide sequence, and for additional nucleic acids that hybridize under high and moderate stringency conditions and encode VIP. The additional large number of DNA molecules within the scope of the claims, however, lacks adequate written description. The skilled artisan could not envision the subgenus of DNA molecules that meet the functional limitations of the claims.

Therefore, given the unpredictability of the art, the broad nature of the disclosure, and the limited number of specific examples of structures that meet the claim limitations, the artisan would not be able to envision the invention based upon the description provided and, therefore, would not conclude that applicants were in possession of the invention at the time the specification was filed.

Claim 10 is rejected under 35 U.S.C. § 112, first paragraph, as being based on insufficient enabling disclosure in the specification and for failure to satisfy the best mode requirement. The claim covers all mutants of the XOX cell line which produce ''increased amounts" of VIP. There is insufficient disclosure in the specification to support the breadth of this claim. Also, the art of producing cell mutants is known to be unpredictable and nonreproducible. Thus, the specification does not teach those skilled in the art how to make or use the best mode of this invention. Deposit of mutant cell line XOXE is required to meet the best mode requirement. Furthermore, deposit of the mutant cell line is required since the mutant cell line could not be obtained without undue experimentation.

Claims 1-12 are rejected under 35 U.S.C. § 112, second, as being indefinite. The terms "anti-viral activity" (in claims 1, 3 and 5), “capable of” (claims 5 and 6), "anti-virally effective amount" and "biological equivalent" (in claims 7-9) "increased amounts" (in claim 10), are vague and indefinite.

35 U.S.C. § 102 reads in relevant part as follows:

"A person shall be entitled to a patent unless-

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, .

Claims 1-4 and 9 are rejected under 35 U.S.C. § 102(b) as being anticipated by the Anglin et al. article cited in the BACKGROUND section of the present application. Claims 1 and 2 are so broad as to read on the DNA and protein naturally occurring in the XOX cells used by Anglin et al. Claims 5 and 6 are so broad as to read on Anglin et al.'s use of XOX cell supernatants to treat PDQ-infected XBX cells.

35 U.S.C. § 103(a) reads in relevant part:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims 5-8 are rejected under 35 U.S.C. § 103(a) as being obvious from the Anglin et al. article. Anglin et al. teach that XOX cell supernatants contain a protein useful in the treatment of PDQ virus infection. It would have been obvious to one skilled in the art at the filing date of the present application to purify the protein by well-known techniques such as HPLC (or to make it by recombinant means) and use the protein for the purposes described in Anglin et al.

Signed:

Examiner Tough

**Please draft a new set of claims and provide arguments for overcoming the rejections. Please note any supporting documents that need to be submitted.**

**Biotechnology**

**Amendment Writing**

**Homework Problem #2**

**Biotech Problem II**

Attached is the specification and pending claims in an application directed to M-CSF antibodies. The application was filed on January 1, 2019. Draft a response to the following rejections raised in a first Office Action issued in the application.

1. Claims 1-5 are rejected under 35 U.S.C. §112(a) for lack of written description. While the specification describes the antibody prepared in Example 1, it does not describe all antibodies having the recited Kd and Koff values. The inventors have, therefore, not shown possession of the full scope of the claimed invention at the time of filing.

2. Claims 1-5 are rejected under 35 U.S.C. §112(a) for lack of enablement. While the specification describes the antibody prepared in Example 1, it does not describe how to make all antibodies having the recited Kd and Koff values. The genus recited in the claims potentially encompasses thousands of antibodies. Only one specific antibody is described and exemplified in the application. Little guidance is provided in the specification for finding other antibodies having the claimed properties. Furthermore, the art of antibody preparation is unpredictable. Thus, one of ordinary skill in the art would require undue experimentation to make all of the claimed antibodies.

3. Claims 1-5 are rejected under 35 U.S.C. §103(a) as obvious over Quack in view of Honk. Quack teaches that M-CSF is a known antigen target for treating cancer. Honk teaches how to obtain antibodies to an antigen target by using phage display technology. A person of ordinary skill in the art would have been motivated to generate antibodies to M-CSF by Quack, and have had a reasonable expectation of success for doing so by phage display based on Honk. The exemplified M-CSF antibody in the application was prepared by phage display technology. It would have therefore been obvious based on Quack and Honk to prepare the claimed M-CSF antibodies.

**M-CSF Antibodies**

Background of the Invention

Macrophage colony stimulating factor (M-CSF) is a member of the family of proteins referred to as colony stimulating factors (CSFs). M-CSF is a secreted or a cell surface glycoprotein comprised of two subunits that are joined by a disulfide bond with a total molecular mass varying from 40 to 90 kD. Similar to other CSFs, M-CSF is produced by macrophages, monocytes, and human joint tissue cells, such as chondrocytes and synovial fibroblasts, in response to proteins such as interleukin-1 or tumor necrosis factor-alpha. M-CSF stimulates the formation of macrophage colonies from pluripotent hematopoietic progenitor stem cells.

M-CSF typically bind to its receptor, c-fms, in order to exert a biological effect. c-fms contains five extracellular Ig domains, one transmembrane domain, and an intracellular domain with two kinase domains. Upon M-CSF binding to c-fms, the receptor homo-dimerizes and initiates a cascade of signal transduction pathways including the JAK/STAT, PI3K, and ERK pathways.

M-CSF is an important regulator of the function, activation, and survival of monocytes/macrophages. A number of animal models have confirmed the role of M-CSF in various diseases, including rheumatoid arthritis (RA) and cancer.

There is a need for therapeutic anti-M-CSF antibodies.

Summary of the Invention

The present invention provides isolated human antibodies or antigen-binding portions thereof that specifically bind human M-CSF and acts as a M-CSF antagonist and compositions comprising said antibody or portion. Structural similarities between M-CSF and other CSF family members complicate the task of eliciting a M-CSF antibody that neutralizes M-CSF but not GM-CSF and G-CSF. Furthermore, M-CSF is highly conserved across species. Similarity in the receptor binding domain of mouse M-CSF and human M-CSF further complicate the generation of neutralizing anti-human M-CSF antibodies in available mouse models.

The invention also provides for compositions comprising the heavy and/or light chain, the variable regions thereof, or antigen-binding portions thereof an anti-M-CSF antibody, or nucleic acid molecules encoding an antibody, antibody chain or variable region thereof the invention effective in such treatment and a pharmaceutically acceptable carrier. In certain embodiments, the compositions may further comprise another component, such as a therapeutic agent or a diagnostic agent. Diagnostic and therapeutic methods are also provided by the invention. In certain embodiments, the compositions are used in a therapeutically effective amount necessary to treat or prevent a particular disease or condition.

The invention also provides methods for treating or preventing a variety of diseases and conditions such as, but not limited to, inflammation, cancer, atherogenesis, neurological disorders and cardiac disorders with an effective amount of an anti-M-CSF antibody of the invention, or antigen binding portion thereof, nucleic acids encoding said antibody, or heavy and/or light chain, the variable regions, or antigen-binding portions thereof.

The invention provides isolated cell lines, such as a hybridomas, that produce anti-M-CSF antibodies or antigen-binding portions thereof.

The invention also provides nucleic acid molecules encoding the heavy and/or light chains of anti-M-CSF antibodies, the variable regions thereof, or the antigen-binding portions thereof.

The invention provides vectors and host cells comprising the nucleic acid molecules, as well as methods of recombinantly producing the polypeptides encoded by the nucleic acid molecules.

Detailed Description of the Invention

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The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix.

The term "Kd" refers to the equilibrium dissociation constant of a particular antibody-antigen interaction.

Example 1 - Preparation of M-CSF Antibody By Phage Display

…

The antibody prepared has the VL and VH amino acid sequences provided shown in SEQ ID NO: 1 and SEQ ID NO: 2.

Example 2 - Kinetic Analysis of Binding of Human Antibodies to M-CSF

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Example 3 - Alanine Scanning Mutagenesis of CDR3 Domains

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Claims:

1. An isolated human antibody, or an antigen-binding portion thereof, that dissociates from human M-CSF with a Kd of 1 \* 10-7 M or less and a Koff rate constant of 1 \* 10-3 s-1 or less, both determined by surface plasmon resonance, and neutralizes human C-MSF cytotoxicity in a standard in vitro K535 assay with an IC50 of 1 \* 10-7 M or less.

2. The isolated human antibody, or antigen-binding portion thereof, of claim 1, which dissociates from human M-CSF with a Koff rate constant of 5 \* 10-4 s-1 or less.

3. A human monoclonal antibody or an antigen-binding portion thereof that specifically binds to M-CSF, wherein the antibody or portion possesses at least one of the following properties: a) binds to human secreted isoforms of M-CSF and membrane bound isoforms of M-CSF; b) has a selectivity for M-CSF that is at least 100 times greater than its selectivity for GM-CSF or G-CSF; c) binds to M-CSF with a Kd of 1.0 \* 10-7 M or less; d) has an off rate (koff) for M-CSF of 2.0 \* 10-4 s-1 or smaller; or e) binds human M-CSF in the presence of human c-fms.

4. An isolated human antibody, or antigen-binding portion thereof, with the following characteristics:

a) dissociates from M-CSF with a Koff rate constant of 1 \* 10-3 s-1 or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 12 or 15 or by one to five conservative amino acid substitutions at positions 2-10 and 16-20;   
c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 3-12 or by one to five conservative amino acid substitutions at positions 3-12.

5. An isolated human antibody having a light chain CDR3 domain comprising a sequence that has at least 92% identity to the amino acid sequence set forth in SEQ ID NO: 3 and a heavy chain CDR3 domain comprising a sequence that has at least 92% identity to the amino acid sequence set forth in SEQ ID NO: 4, wherein the antibody specifically binds to M-CSF.