IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of : :

Pieczenik : Group Art Unit 1631

Serial No. 09/193,390

: Examiner: John Brusca

For: METHOD AND MEANS FOR SORTING :
AND IDENTIFYING BIOLOGICAL
INFORMATION

APPEAL BRIEF

Prepared by

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A- CLAIMS IN CONSIDERATION

B- DISCLOSURE DOCUMENT 118831 JULY 11, 1983 AND TYPED VERSION

C- PROF. NORTON ZINDER'S LETTER OF ANALYSIS OF ENABLEMENT AND PRIORITY DECEMBER 21,2001

I-REAL PARTY OF INTEREST- The real party of interest is the inventor, Dr. George Pieczenik, applicant, pro se

II- RELATED APPEALS AND INTEFERENCES- I am unaware of any related appeals and inteferences

III-STATUS OF CLAIMS- Claims 29-65 are rejected

IV-STATUS OF AMENDMENTS- Preliminary amendment filed by previous attorney Shawn P.Foley , dated June 11, 1999 and received 6/16/1999 by Examiner John Brusca. Amendment was entered. Brusca stated "**THIS ACTION IS MADE FINAL** even though it is a first action after the filing". This amendment will be the basis of this appeal (Appendix A).

V-SUMMARY OF THE INVENTION

The invention disclosed herein is a population of oligonucleotides and vectors useful in the determination of the epitope, or binding site, of an antigen by an antibody. The oligonucleotides of the present invention encode peptide sequences which are 4-12 amino acids long and do not necessarily stimulate production of antibodies by themselves. Because the encoded peptide sequences are capable of binding with antibodies isolated from lymphoid-derived cells not stimulated by immunization with a particular antigen, the antibodies can be isolated from lymphoid cells that produce a wide variety of antibodies. The competitive binding of a test antigen with a peptide- binding pair identifies the epitope of the test antigen.

The epitope of an antigen is typically determined by producing antibodies to the particular antigen, generating peptides representative of various portions of the antigen, and running competitive binding assays to determine which peptides interfere with binding of the antigen to the antibody. Alternatively, antibodies are produced against various regions of the antigen, then tested against the whole antigen to determine crossreactivity. - Both of the above methods assume that the antigenic region and the binding site of the antigen are one and the same. Accordingly, each of the prior art methods is dependent on the production of antibodies against the antigen. These methods also require some knowledge about the antigen and its purification, either its sequence or the sequence of its antigenic regions, in order to run competitive binding assays.

The present invention is novel in that it separates the antigenic or immune-response stimulating character of an antigen from the binding character of the antigen. In doing so, it provides

the capability, previously unknown in the art, to determine the epitope of an antigen even if the antigen has not been isolated and no antibodies to the antigen are available. Because the invention does not require an immune response, the claimed peptides can be paired with antibodies isolated from cells of non-immunized organisms, including humans. Furthermore, because the oligonucleotides of the present invention encode peptides that are representative of all the peptide sequences that can possibly exist for a particular length, the epitope of an unidentified antigen can be determined absent any knowledge regarding the nature of the antigen, its amino acid sequence, or the gene responsible for its production.

Applicant has amended the specification to update the status of the parent applications. The remaining originally filed claims have been canceled. New claims 29-65 have been added (Appendice A). Claims 29-49 are directed to recombinant vector populations and methods of using the recombinant vector populations to produce populations of epitopic peptide sequences. These claims correspond to like claims set forth in Applicant's U.S. Patent No. 5,866,363 which issued from parent application no. 662,764, except that the recombinant vector has been defined in terms of a filamentous bacteriophage. This recitation is set forth in claim 17 of the parent application no. 662,764. Claims 41, 42 and 43 further define the bacteriophage as f1, fd and M 13 respectively. Support for those recitations is set forth on page 8, line 24 of the ‘764 application. Claims 50-62 are directed to a discrete population of antibodies, support for which is set forth in claims 22-27 of the '764 application and in the paragraph bridging pages 8-9 of the ‘764 application. Claims 63-65 are directed to a method of making the discrete population of antibodies and which correspond substantially to claims 22-24 of the ‘764 application. Accordingly, no new matter has been added.

VI-ISSUES

(1) Priority Issues-Whether the continuing application is for a patent for an invention, which is also disclosed, in the first application (the parent or provisional application.

(2) Priority Issues- Whether the instant claims 29-49 drawn to filamentous phages and their method of use are disclosed in parent Applications 07/201358 and 06/770390.

(3) Whether there is sufficient disclosure in Parent Application filed August 27, 1985 to enable what has now become known as phage display.

(4) Priority Issues-Whether prior art published before the filing date of parent Application No.07/662764 has been properly applied.

(5) Whether the Foreign filing publication EP O 241 487, on 21 October 1987 , of Dr. Pieczenik's Parent Application 06/770390 which is prior to the references Oliphant et al and Parmley et al, which are cited by Examiner obviates their use as a prior art ,obviousness and/or anticipation rejections.

(6) Whether Claims 29-43, 46-49, and 65 are indefinite as not claiming the subject matter in regards to the invention as proscribed in 35 USC § 112.

(7) Whether Claims 29,31-40,42, and 44-49, drawn to libraries of filamentous phage vectors, are unpatentable as obvious over Parmley et al in view of Oliphant et al as proscribed in 35 USC § 103.

(8) Whether Claims 30 and 50-62 are obvious and unpatentable under 35 USC 103 (a) over Parmley et al in view of Oliphant et al and Winger et al.

(9) Whether Claim 41 and 43, drawn to filamentous phage f1 and M13, are obvious and unpatentable under 35 USC§ 103 (a) over Parmley et al. in view of Oliphant et al and Smith in view of Horiuchi et al.

(10) Whether Claims 63-64 , drawn to a method of making a paired population of antibodies and epitopes, are obvious and unpatentable under 35 USC § 103 (a) over Parmley et al in view of Oliphant et al and Winger et al.

(11) Whether Claim 65, drawn to a method of lymph cells that are derived from a fetus or a neonate, is obvious and unpatentable under 35 USC § 103 (a) over Parmley et al. in view of Oliphant, Winger and Reading.

VII-GROUPING OF CLAIMS

Claims 29-49 have been rejected under 35 U.S.C. § 120 as not also being disclosed in the parent application. Claims 29-49 are to be treated as a unit with respect to this rejection.

Claims 29-43, 46-49 and 65 have been rejected under 35 U.S.C. § 112 as being indefinite. Claims 29-43, 46-49 and 65 are to be treated as a unit with respect to this rejection.

Claims 29, 31-40, 42 and 44-49, drawn to libraries of filamentous phage vector and some embodiments fd, have been rejected under 35 U.S.C. § 103 (a) as being obvious over Parmley et al in view of Oliphant et al. Claims 29, 31-40, 42 and 44-49 are to be treated as a unit with respect to this rejection.

Claims 30 and 50-62, drawn to vectors bound by non elicited antibodies, are rejected under 35 U.S.C. § 103(a) as being obvious over Parmley et al in view of Oliphant and Winger et al. Claims 30 and 50-62 are to be treated as a unit with respect to this rejection.

Claims 41 and 43, drawn to filamentous vectors f1 and M13, are rejected under 35 U.S.C. § 103 (a) as being obvious over Parmley in view of Oliphant and Smith in view of Horiuchi. Claims 41 and 43 are to be treated as a unit with respect to this rejection.

Claims 63-64, drawn to a population of antibodies that recognize peptide epitopes, are rejected under 35 U.S.C § 103(a) as being obvious over Parmley in view of Oliphant and Winger in view of Reading. Claims 63 and 64 are to be treated as a unit with respect to this rejection.

Claim 65, drawn to lymph cells that are derived from a fetus or a neonate, is rejected under 35 U.S.C § 103(a) as being obvious over Parmley et al. in view of Oliphant et al. and Winger in view of Reading..

VIII-ARGUMENT

A. Priority Issues-

Whether the continuing application is for a patent for an invention which is also disclosed in the first application (the parent or provisional application). Whether the instant claims 29-49 drawn to filamentous phages and their method of use are disclosed in parent Applications 07/201358 and 06/770390. Whether there is sufficient disclosure in Parent Application filed August 27, 1985 to enable what has now become known as phage display. Whether prior art published before the filing date of parent Application No.07/662764 has been properly applied.

I argue these issues as a group:

Applicant has complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C § 120

> *Benefit of earlier filing date in the United States. An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.*

and with the requirements of the first paragraph of 35 U.S.C. § 112.

> *USC 35 112 Specification. 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. The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

Applicant has given a written description of the invention in his specification of parent Applications 07/201358 and 06/770390, and of the manner and process of making and using it,

in 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 as required in 35 U.S.C. § 112 first paragraph.

In addition, applicant having complied with 35 U.S.C. § 112 first paragraph is, thereby, entitled to the benefit of the earlier filing date in the United States because the application for the patent for the invention was disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States ie 06/770390, or as provided by section 363 of this title, which was filed by the inventor named in the previously filed application. Therefore, in order to comply with 35 U.S.C § 120 the applicant shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

Specifications in continuing application at issue were disclosed in the parent application and in the European Filing of the parent application. The European filing published on 21 October 1987 as number EP 0 241 487. A Disclosure Document No 118831 was filed on July 11, 1983 (Appendix B). The parent application filed August 27, 1985 and issued as US patent No. 5,866,363 on Feb 2, 1999. This application and patent took over 14 years to prosecute and issue.. Applicant and previous supervisor George Eliot believe that this patent should have issued earlier and that this delay was a consequence of patent office policy and other patent office reasons.

Appendix C is a letter from Prof. Norton Zinder, in whose laboratory filamentous bacteriophage were discovered. He states that the original filing has all the information necessary to make a display vector from f1 bacteriophage. In this letter he compares the original filing August 27, 2001, 06/770390, to the issued patent US 5,866,363, Feb. 2, 1999 and shows where all the elements and specifications necessary for enablement in 1985 and priority in 1985 are disclosed and identical.

The specific elements of this identity are shown below:

The term " Original" refers to August 27, 1985 filing and specifications, filing 06/770390.

They are: p. 5 Original 1985 Filing and '363 Column 4 lines 37-42 In preferred embodiments each

member of the insert population has a single copy of the sequence of nucleotide triplets, and the insert has between 5 and 7 triplets: the replicating sequence can be a plasmid such as pBR322, a virus, such as lambda-gt 11 or vaccinia, or a filamentous bacteriophage (emphasis added)

P. 7 Original 1985 Filing 'An epitope is a specific site **on the surface of an antigen** that is recognized by an antibody. 363 Column 5 line 43-45 The invention permits the identification of **the specific peptide sequence on a protein that is recognized by an antibody, i.e., the epitope.**

p.13 Original 1985 Filing '363 Column 81ines 56-65 The nucleotide sequence must be inserted at a location in the vector where it will be translated in phase when the vector is transferred into an appropriate host cell, and where it will not interfere with the replication of the vector under the experimental conditions employed, i.e. the nucleotide sequence must be inserted into a non-essential region of the vector. Pieczenik US Patent 4,359,535 and 4,528,266 hereby incorporated by reference, disclose a method for inserting foreign DNA into a non-essential region of a vector.

p.13 Original 1985 Filing '363 Column 9, lines 11-41, 59-67, Column 10 lines 1-23

The nucleotide sequence is advantageously inserted in such a way that the peptide sequence is expressed on the **outside surface of the vector.** To prepare inserts having these characteristics, an appropriate vector, e.g. a phage or plasmid is first selected. The vector is then randomly cleaved according to the method disclosed in Pieczenik, U.S. Patent 4,359,535 and 4,528,266 to yield a population of linear DNA molecules having circularly permuted sequences. After the cleavage steps, a synthetic oligonucleotide linker bearing a unique nucleotide sequence to both ends of each linearized vector by blunt end ligation. The random linears can then be treated with restriction endonuclease specific to the attached sequences, to generate cohesive ends.

DNA encoding a gene product, eg human hemoglobin, not present in the vector, is fractionated to the desired size eg, fifteen nucleotides long and the nucleotide sequences ligated to the same type of linker used with the random linears. The fractionated nucleotide sequences are then inserted into the random linears and the modified vectors are transferred into appropriate host cells. The host cells are diluted, plated and the individual colonies grown up. On replica plates, the colonies are screened with a monoclonal or polyclonal antibody specific to the gene product.

A positive reaction with the antibody identifies a colony wherein the inserted nucleotide sequence is translated in phase, and the encoded peptide sequence is **on the outside surface** of the polypeptide or

protein, **accessible to the antibody screening** assay. If the monoclonal antibody is employed in the screening step, then this procedure will identify only those colonies where the specific peptide sequence comprising the site recognized by that antibody is inserted **on the outside surface of the polypeptide or protein.** If a polyclonal antibody is employed, or a mixture of several monoclonals, then any colony containing on the outside surface of the polypeptide or protein any peptide sequence insert comprising a recognition site of the foreign gene product will be identified. This procedure identifies vectors that can be advantageously used in the present invention.

p.15 Original , '363 page 11lines 3-5 The **peptide sequence** itself can serve as a sensitive biological tag where it occurs **on the surface of a protein or vector**.

The procedures given above are and were sufficient for any one of ordinary skill in the art in 1985, such as the members of the Zinder laboratory at that time ie Model, Horuichi and Vovis, who are cited by the Examiner as Horiuci et al to make and isolate a display phage from f I bacteriophage. It was known at the time that the surface proteins of f I bacteriophage were gene III and gene VIII. That is the sum of the proteins of the bacteriophage itself. Therefore, the procedure above would have necessarily yielded display phage with foreign inserts in gene III and gene VIII. This letter is sufficient evidence that display phage, particularly f1, as they are now known and phage also displaying combinatorial libraries as they are now known were conceived and enabled in 1985 with the filing of the patent application. This is necessarily the case in that patent filings are to be considered reduction to practice in the U.S. The applicant therefore argues that he receive the benefit of the earliest prior date filing date for issues of priority, non-obviousness, definiteness and enablement.

In terms of priority on Claim 64, drawn to the aseptically raised, fetal or neonatal animals as a source of a "naïve" antibody library, examiner incorrectly states that:

> *"instant claim 64 drawn to a method using lymph cells prepared from mammals **raised in an antiseptic environment was not disclosed** in parent Applications 07/201358 and 06/770390".*

Applicant respectfully suggest that Page 10 of 06/770390 (1985 filing) lines 18-23 contradict examiners contention: Applicant clearly states :

> *p.10 Antibodies produced by the hybridomas derived from the spleen cells of mature animals that were **raised aseptically or from fetal or neonatal animals***

will not reflect any exposure history and can be expected to represent a random sample of the full range of antibodies that the animals are capable of producing."

p.25 Alternatively, spleen cells are harvested from mice that have not been antigenically stimulated.

Therefore, applicant respectfully requests the prior filing date for the claims 64 as having complied with the requirements of 35 U.S.C §112 and 35 U.S.C. § 120 in terms of claim 64.

Another reason to award the applicant the earliest filing date for priority arises from the fact that this Application has been in prosecution for 14 years and has thereby created a Catch 22 situation. The Foreign Filing publication date now predates the most important and repeated of the prior art references, particularly Parmley et al and Oliphant et al. In specific, all of the examiners references concerning phage display of epitopic library on anticipation, obviousness and priority are after applicants European Patent Office Publication Date of 21 October 1987. EP 0 241 487 "Method and Means for Sorting and Identifying Biological Information". (Contracting States are AT, BE., CH, DE, FR, GB, IT, LI, LU, NL, SE.) Therefore, in general, the priority argument against applicant should be made moot. There is a very important principle of jurisprudence which states ***Nunc Pro Tunc***. The examiner has been forced to Nunc Pro Tunc the application by invoking application specification 07/662764 as prior date (filed 2/28/91) rather than 06/770390. This creates the legal paradox that the patent application itself, in the guise of its foreign filing publication, predates itself as prior art. This creates a logical inconsistency. This is why the principle of ***Nunc Pro Tunc*** is invoked to avoid logical inconsistencies.

6) Whether Claims 29-43, 46-49, and 65 are indefinite as not claiming the subject matter in regards to the invention as proscribed in 35 USC § 112.

Examiner states that claims 29-43 and 46 are indefinite "because it is not clear whether the claimed filamentous phage or the product of the method of making filamentous phage comprise a single

member of an oligonucleotide population or a plurality of different members of an oligonucleotide population. The rejection would be overcome by amending claims 29 and 46 to clearly limit the filamentous phage to comprise a plurality of different members of an oligonucleotide population. Applicant agrees with the Examiner and respectfully accepts his recommendation in this instant. Under MPEP § 707.07(j) the now pro se Applicant respectfully requests that if the Examiner finds patentable subject matter disclosed in this application, but feels that Applicant's present claims are not entirely suitable, the Examiner draft more allowable claims for applicant.

7) Whether Claims 29,31-40,42, and 44-49, drawn to libraries of filamentous phage vectors, are unpatentable as obvious over Parmley et al in view of Oliphant et al as proscribed in 35 USC § 103.

All the obviousness rejections set forth by examiner are based on 35 USC § 103 which states:

> *a) 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 difference between the subject mater sought to be patented and 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.*

We argue that for a reference to anticipate a claim under Section 102, the reference must show each and every element or limitation of a claim. This is similar to a request for an interference. Hybridtech v. Monoclonal Antibodies, 231 U.S.P.Q. 81 (Fed. Cir.1986). Atlas Powder Co. v. E.I. du Pont de Nemours &Co., 224 U.S.P.Q. 409, 411 (Fed. Cir . 1984 ('exclusion of a claimed element from a prior art reference is enough to negate anticipation by that reference").

The cited references Parmley et al in view of Oliphant do not disclose every element of claims 29, 31-40, 42 and 44-49 and, therefore, do not anticipate the claimed invention. The examine argues that Parmley shows "in the abstract and throughout an fd filamentous phage vector comprising an insertion in gene III of an antigenic epitope and methods of screening libraries comprising such vectors that express the epitope on choice."

The abstract only discloses the phrase "antibody-selectable" vectors. No specific claim elements are disclosed. The body of the paper discusses isolating vectors containing a known epitope against a background of wild type bacteriophage f1. The epitope inserted was the lacZ and its coding of ß galactosidase. The antibody they used was an anti- ß

galactosidase. There is no recitation of a population of epitopes nor a population of antibodies. Parmley discusses an "epitope library" containing 6 amino acid epitopes or a population of 64 million. Besides the fact that this specific library was disclosed in applicants foreign filing one year prior to Parmley's publication this does not disclose every element in each of claims 29, 31-40, 42, and 44-49. In addition, Parmley et al suggests making such a library without any direction on how to do such. Examiner apparently believes that the claimed vector library population in claim 29, 31-40, 42 and 44049 are inherent in the library discussed in Parmley et al. In order for prior art to anticipate the claimed population of 4-12 amino acid epitopes on the ground of inherency, the inherency must be certain. Ex parte Cyba, 155 U.S.P.Q 756 (P.T.O. Bd. App. 1958), Ethyl Molded Products Co.v Betts Package Inc. 9 U.S.P.Q.2d 1001, 1032-33 (E.D.Ky.1988) (the inherency doctrine is " available only when the prior inherent event can be established as a certainty. That any event may result from a given set of circumstances is not sufficient to establish anticipation. Probabilities are not sufficient.") Phillips Petroleum Co. v. U.S. Steel Corp., 9U.S.P.Q.2d 1461 (Fed. Cir. 1089)(" Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references."); and Ex parte Skinner, 2 not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In the present instance, any identity between the Parmley libraries and those claimed is purely speculative, not certain or necessary. Thus, the reference cannot be used to reject Claims 29, 31-40, 42, and 44-49 under the "inherency doctrine." Oliphant do not disclose elements of claims 29,31-40,42, and 44-49 which require random synthesis of "coding regions" that consists of lengths of about 4 to about 12 nucleotide triplets. The random sequences Oliphant discloses are not translated into peptides and are not a multiple of triplets when inserted. They are 14 nucleotides long. We repeat our argument of above that for a reference to anticipate a claim under Section 102, the reference must show each and every element or limitation of a claim. This is similar to a request for an interference. Hybridtech v. Monoclonal Antibodies, 231 U.S.P.Q. 81 (Fed. Cir.1986). Atlas Powder Co. v. E.I. du Pont de Nemours &Co., 224 U.S.P.Q. 409, 411 (Fed. Cir . 1984 ('exclusion of a claimed element from a prior art reference is enough to negate anticipation by that reference").

8) Whether Claims 30 and 50-62, vectors bound by antibodies, are unpatentable as obvious over

Parmley et al in view of Oliphant et al and further in view of Winger et al. as proscribed in 35 USC § 103(a).

Arguments relating to Parmley et al in view of Oliphant et al repeat arguments given above. The Winger et al reference only claims "monoclonal Epstein-Barr virus transformants" producing specific antibody to a variety of antigens without prior deliberate immunization. Winger uses adult peripheral cells isolated from leukophoresis-separated "buffy coat" fractions obtained from **adult platelet donors.** This population only can create a very limited number of antibodies. Only those antibodies made are to the **antigens that the adult donors have been exposed.** This unimmunized population of adult donors reflect the exposure history of the adults. They have been inadvertently immunized in the course of living**.** This population of antibodies is not the population claimed in claim 30 or 50-62. The antibody population claimed requires at least 10% of the binding population of epitopes made as described in the specifications. In one aspect the antibodies produced by the hybridomas derived from the spleen cells of mature animals that were **raised aseptically or from fetal or neonatal animals** will not reflect any exposure history and can be expected to represent a random sample of the full range of antibodies that the animals are capable of producing. Winger et al does not teach or anticipate this population of antibodies. In addition, making monoclonals with Epstein-Barr virus fusion makes the antibodies derived suspect to contamination with Epstein Barr virus which obviate their use for the utility of the present invention.

9) Examiner states that Winger et al shows on page 4487 that their method allows for the generation of an antibody of a desired specificity. These are only antibodies that exist as a consequence of the exposure history of the adult. It is not a full repertoire of antibodies, or even a representative sample of the repertoire of antibodies. We repeat our arguments and citations on inherency cited above. ." In the present instance, any identity between the Winger's Epstein-Barr monoclonal transformants and the population of binding antibodies claimed is purely speculative, not certain or necessary. Thus, the reference cannot be used to reject Claims 30 and 50-62 under the "inherency doctrine." In addition, Winger does not recite any elements in the claims 30and 50-62. Therefore, claims 30 and 50-62 should be allowed as patentable under 35 USC § 103(a).

10) Whether Claim 41 and 43, drawn to filamentous phage f1 and M13, are obvious and unpatentable under 35 USC§ 103 (a) over Parmley et al. in view of Oliphant et al and Smith in view of Horiuchi et al. We argue that for a reference to anticipate a claim under Section 102, the reference must show each and every element or limitation of a claim. This is similar to a request for an interference. Hybridtech v. Monoclonal Antibodies, 231 U.S.P.Q. 81 (Fed. Cir.1986). Atlas Powder Co. v. E.I. du Pont de Nemours &Co., 224 U.S.P.Q. 409, 411 (Fed. Cir . 1984 ('exclusion of a claimed element from a prior art reference is enough to negate anticipation by that reference"). Examiner rightful states that Parmley et al in view of Oliphant does not show use of f1 or M13 and therefore does not recite a necessary element of claim 41 and 43.

Smith shows use of an f1 filamentous phage to express a large nucleotide sequence (132 base pairs) of Eco R1 endonuclease coding and the ability of an antibody to Eco R1 to "enhance" the proportion of this phage in a population. However, Smith does not show a Western protein blot to demonstrate that the insertion was actually in gene III. Gene III was not isolated or purified nor was the fusion product isolated or purified. It was assumed to have inserted correctly and expressed. It is also a very large insert and the region of antibody binding is not defined. The insertion itself, nor the site of binding on the large insert expressed was never directly demonstrated. Pieczenik, in his specifications and invention, has demonstrated by Western blot the actual insertion of an epitope that is 5 amino acids long in gene III of f1 bacteriophage. This was the first such direct demonstration of an epitope inserted in gene III. Not a much larger sequence containing a possible epitope as shown in Smith. In addition, there is no anticipation of using smaller sequences by Smith in this paper. This would be required as to make 132 base pair random sequences would be impossible.

Again we argue that the Claims of 41 and 43 on use of f1 and M13 as epitope expression vectors was not anticipated and is not obvious in view of Smith.

Examiner cites Horiuci et al as prior art on the similarity between M13, f1, and fd. However, this similarity is their "genetic map" deduced by complementation and not by sequence. In fact, M13 and f1 differ from each other by at least 100 nucleotides and more specifically, there is a Bam site in f1 in gene III that does not exist in M13. Therefore, one

can insert into gene III of f1 by using Bam cleavage. M13 would require manipulation to make a similar vector. So they are from the point of view of display vector design functionally different.

In addition, I attach the support letter of Prof. Norton Zinder, Appendice C. Prof. Zinder's laboratory is the place f1 was discovered and is the foremost authority on this phage. Horiuchi, Vovis and Model (Horiuchi et al) cited by examiner have been junior staff and post docs in Prof.Zinder's laboratory.

. Therefore, claims 41 and 43 should be allowed as patentable under 35 USC § 103(a).

11) Whether Claims 63-64 , drawn to a method of making a paired population of antibodies and epitopes, are obvious and unpatentable under 35 USC § 103 (a) over Parmley et al in view of Oliphant et al and Winger et al. and Reading

Parmley et al in view of Oliphant et al and Winger et al are argued above. Reading et al is to be discussed.

Examiner correctly states that the above reference do not teach fusion of lymph cells with myeloma cells or animals raised in an antiseptic environment. Examiner incorrectly states that Reading "teaches a method of generating monoclonal antibody producing cells by fusing lymph cells from unimmunized animals to myeloma cells (see pages 275-280)". This is incorrect. Page 275 is titled "Immunizations". Then it continues to describe in detail immunization procedures. Therefore, Reading does not anticipate any "naïve" or unimmunized antibody libraries.

Therefore, claims 63-64 should be allowed as patentable under 35 USC § 103(a).

12) Whether Claim 65, drawn to a method of lymph cells that are derived from a fetus or a neonate, is obvious and unpatentable under 35 USC § 103 (a) over Parmley et al. in view of Oliphant, Winger and Reading. Examiner states that Denis et al pages 53-57 show a method to make monoclonal antibody secreting hybridoma cells derived from murine neonate spleen cells.

Denis et al recite making monoclonal antibodies to a specifically induced antigen in neonatal splenic fragment cultures. The antibodies are made to DNP-hemocyanin. The monoclonal antibody made is anti-DNP antibody. Denis et al refers only to an immunized neonate not an unimmunized neonate. Therefore, there is no anticipation of claim 65 which is dependent on claim 63 which has the element of "lymph cells **that have not been antigenically stimulated with a particular antigen**".

Therefore, repeat citations and arguments above concerning anticipating of claim elements . In addition, the Examiner needing to combine five separate references (Parmley et al, Oliphant et al, Winger et al, Reading et al and Denis et al) to demonstrate obviousness seems to suggest just the opposite, non-obviousness. The Court of Appeals for the Federal Circuit held in In re Jones, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992):

> *Before the PTO may combine the disclosure of two or more prior art references in order to establish prima facie obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art In re Fine , 837 F.2d 1071, 1074, 5 USPQ2d 1596 (Fed. Cir. 1988)*

Therefore, claims 65 should be allowed as patentable under 35 USC § 103(a).

IX- CONCLUSION

The prior date argument are improper in that all elements of all claims appear in the original filing as well as the issued patent and the amended specifications. This has been demonstrated by the Applicant and also by a support letter from the father of phage transduction, Norton Zinder. Specifications in the original filings allow anyone of ordinary skill in the art to conceive, make and produce display vectors from filamentous bacteriophage as of 1985 with specific insertion within gene III and gene VIII of f1 bacteriophage and related phage of combinatorial peptide libraries. In addition, all the specifications and novelty of making "naïve" antibody libraries had been described in the 1985 filing. In addition, the pairing of these two libraries, epitopic and antibody, is also described in the original filings. Therefore all the claims at issue 29-65 should be given a priority related to the original filing. This would also obviate the legal inconsistency of a foreign publication of a US patent being effectively prior art to itself.

The obviousness rejections have been addressed and do not stand under careful examination. Parmley et al and Oliphant et al do not anticipate a peptide (epitopic) library comprising a range of peptides from about 4 to about 12 amino acids or a proportion thereof. Parmley et al and Oliphant et al in view of Winger do not anticipate pairs of antibodies (derived from non-immunized mammals) and the peptide library above. Reading et al is irrelevant as it discusses immunized animals. Denis et al discusses neonates but only immunized neonates. Therefore, none of the references cited or combinations thereof , anticipate creating a large repertoire of antibodies from neonates that can be bound to a population of epitopic peptides displayed on a bacteriophage as individual pairs. This invention allows for the identification of unknown molecular surfaces in terms of sequence and the identification antibody specificities irrespective of immunization.

This appeal brief is being submitted in triplicate and is accompanied by a check in the amount of $160.00 Filing a brief in support of an appeal is $160.00.
A Petition for Extension of Time for 5 months and the requisite fee of $980.00.Extension for response within fifth month is $980.00.

Respectfully submitted:

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APPENDICE A - PRELIMINARY AMENDMENT AND CLAIMS

PATENT
ICTECH 3.0-002 CIP CONT DIV
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
In re Patent Application of
Pieczenik
ApplicationNo. 09/193,390
Filed; November 18, 1998
For: Method and Means for Sorting and
Identifying Biological Information

Group Art Unit: 1646
Examiner: J. Brusca
Data: June 11, 1999
Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT
Sir:
Prior to examination on the merits, please amend the above-captioned patent application as follows, In the event there are any fees due and owing, the Examiner is hereby authorized to charge Deposit Account No. 12-1095.
IN THE SPECIFICATION:
On page I line 22, please add -'-is a continuation of application no. 07/662,764, filed February 28, 1991, now U.S. Patent No. 5,866,363, which is a-- immediately after “application” and on line 24, please add—now abandoned—immediately after “1988,”.

IN THE CLAIMS: Please cancel claims 6-18, 20, 22-24, 27 and 28,
Please add the following claims.
29. A population of recombinant vectors comprising:
filamentous bacteriophage comprising a recombinant structural gene, each of the structural genes comprising an insert containing one member of an oligonucleotide population,
said oligonucleotide population comprising oligonucleotides comprising a coding region consisting of a length from about 4 to about 12 nucleotide triplets, said oligonucleotide population encoding a plurality of corresponding random peptide sequences of from about 4 to about 12 L-amino acid residues, and
wherein said recombinant structural genes are expressed upon transfer of said recombinant vectors into *Escherichia coli* host calls, and wherein expression of the recombinant structural genes yields polypeptides each polypeptide comprising one of said plurality of corresponding random peptide sequences.

30. The vector population of claim 29 wherein each of the encoded corresponding peptides forms a binding pair with an antibody that has not been elicited by immunization with said peptide or said peptide in conjugated form, said antibody being selected from the group consisting of all antibodies produced by lymphoid-derived antibody-producing cells, where the group of all antibodies together recognizes substantially all epitopic sequences.

31. The recombinant vector population of claim 29, wherein each of said
if members of said oligonucleotide population has a length of from about 4 to 7 nucleotide triplets and the encoded corresponding peptide sequences have a length of from 4 to 7 L-amino acid residues.

32, The recombinant vector population of claim 29, wherein each of said members of said oligonucleotide population has a coding region having a length of 4 nucleotide triplets and the encoded corresponding peptide sequence has a length of 4 amino acid residues.

33. The recombinant vector population of claim 29, wherein each of said members of said oligonucleotide population has a length of 5 nucleotide triplets and the encoded corresponding peptide sequences have a length of 5 L-amino acid residues.

34. The recombinant vector population of claim 29, wherein each of said members of said oligonucleotide population has a coding region having a length of 6 nucleotide triplets and the encoded corresponding peptide sequence has a length of 6 amino acid residues

35. The recombinant vector population of claim 29, wherein each of said members of said oligonucleotide population has a coding region having a length of 7 nucleotide triplets and the encoded corresponding peptide sequence has a length of 7 amino acid residues.

36. The recombinant vector population of claim 29, wherein each of said members of said oligonucleotide population has a coding region having a length of 8 nucleotide triplets and the encoded corresponding peptide sequence has a length of 8 amino acid residues.

37. The recombinant vector population of claim 29, wherein each of said members of said oligonucleotide population has a coding region having a length of 9 nucleotide triplets and the encoded corresponding peptide sequence has a length of 9 amino acid residues.

38.The recombinant vector population of claim 29, wherein each of said It members of said oligonucleotide population has a coding region having a length of 10 nucleotide triplets and the encoded corresponding peptide sequence has a length of 10 amino acid residues.

39. The recombinant vector population of claim 29, wherein each of said members of said oligonucleotide population has a coding region having a length of 11 nucleotide triplets and the encoded corresponding peptide sequence has a length of 11 amino acid residues.

40.The recombinant vector population of claim 29, wherein each of said members of said oligonucleotide population has a coding region having a length of 12 nucleotide triplets and the encoded corresponding peptide sequence has a length of 12 amino acid residues.

41. The recombinant vector population of claim 29 wherein said filamentous bacteriophage are f1.

42. The recombinant vector population of claim 29 wherein said filamentous bacteriophage are fd.

43. The recombinant vector population of claim 29 wherein said filamentous bacteriophage are M13.

44. The recombinant vector population of claim 29 wherein the sum of corresponding peptide sequences encoded by said oligonucleotide population represents at least about 10% of all possible peptide sequences of said length.

45. The recombinant vector population of claim 29 wherein the sum of the corresponding peptide sequences encoded by said oligonucleotide population includes substantially all possible peptide sequences of said length.

46. A method of producing a population of epitopic peptide sequences, comprising:
providing a population of recombinant Escherichia coli cells, each of said cells containing at least one member of a recombinant vector population, each member of said vector population comprising filamentous bacteriophage, said filamentous bacteriophage comprising a recombinant structural gene, each structural gene containing an insert comprising a member of an oligonucleotide population, said oligonucleotide population comprising oligonucleotides comprising a coding region consisting of a length from about 4 to about 12 nucleotide triplets, said oligonucleotide population encoding a plurality of epitopic peptides consisting of random sequences of from about 4 to about 12 L-amino acid residues; and culturing said recombinant Escherichia coli cells to allow expression of said recombinant structural genes such that said epitopic peptide sequences are accessible to antibody recognition.

47. The method of claim 46 wherein the sum of said corresponding epitopic peptide sequences represents substantially all possible peptide sequences of said length.

48. The method of claim 46 wherein the sum of said corresponding epitopic peptide sequences represents at least about 10% of all possible peptide sequences of said length.

49. The method of claim 48 wherein said oligonucleotide population encodes a number of peptide sequences of said length having sufficient conformational similarity with an antibody binding site of a test species such that an antibody that binds to the antibody binding site of the test species also binds a peptide of the encoded plurality of peptides.

50. A discrete population of antibodies wherein each antibody in said population binds at lent one epitopic peptide in a population of peptides consisting of random sequences of from about 4 to about 12 amino acid residues such that when said population of antibodies and said population of peptides are combined, substantially each member of said population of peptides is bound with an antibody.

51. The population of antibodies of claim 50 wherein said population of peptides consists of random sequences having a length of from about 4 to about 12 amino acid residues and wherein said random sequences represent substantially all possible sequences of said length.

52. The population of antibodies of claim 50 wherein said population of peptides consists of random sequences having a length of from about 4 to about 12 amino acid residues and wherein said random sequences represent at least about ten percent of all possible sequences of said length.

.53. The population of antibodies of claim 50 wherein said population of peptides consists of random sequences having a length of from about 4 to about 7 amino acid residues.

54. The population of antibodies of claim 50 wherein said population of peptides consists of random sequences having a length of 4 amino acid residues.

55. The population of antibodies of claim 50 wherein said population of peptides consists of random sequences having a length of 5 amino acid residues.

56. The population of antibodies of claim 50 wherein said population of peptides consists of random sequences having a length of 6 amino acid residues.

57. The population of antibodies of claim 50 wherein said 1:: peptides consists of random sequences having a length of 7 amino acid residues.

58. The population of antibodies of claim 50 wherein said peptides consists of random sequences having a length of 8 amino acid residues.

59. The population of antibodies of claim 50 wherein said peptides consists of random sequences having a length of 9 amino acid residues.

60. The population of antibodies of claim 50 wherein said population of peptides consists of random sequences having a length of 10 amino acid residues.

61. The population of antibodies of claim 50 wherein said population of peptides consists of random sequences having a length of 11 amino acid residues.

62. The population of antibodies of claim 50 wherein said population of peptides consists of random sequences having a length of 12 amino acid residues.

63. A method of producing a discrete population of antibodies, comprising: harvesting mammalian lymph cells that have not been antigenically stimulated with a particular antigen;

fusing said lymph cells with myeloma cells to produce hybridoma, cells; and

culturing individual hybridoma. cells lines, said cell lines together producing a population of antibodies wherein the antibodies together recognize substantially all epitopic peptide sequences.

64. The method of claim 63 wherein said lymph cells are prepared from mammals raised in an antiseptic environment.

65. The method of claim 63 wherein said lymph cells are harvested from a mammal which is a neonate and a fetus.

REMARKS

Applicant has amended the specification to update the status of the parent applications. The remaining originally filed claims have been canceled. New claims 29-65 have been added. Claims 29-49 are directed to recombinant vector populations and methods of using the recombinant vector populations to produce populations of epitopic peptide sequences. These claims correspond to like claims set forth in Applicant's U.S. Patent No. 5,866,363 (copy enclosed) which issued from parent application no. 662,764, except that the recombinant vector has been defined in terms of a filamentous bacteriophage. This recitation is set forth in claim 17 of the parent application no. 662,764. Claims 41, 42 and 43 further define the bacteriophage as f1 fd and M 13 respectively. Support for those recitations is set forth on page 8, line 24 of the ‘764 application. Claims 50-62 are directed to a discrete population of antibodies, support for which is set forth in claims 22-27 of the '764 application and in the paragraph bridging pages 8-9 of the ‘764 application. Claims 63-65 are directed to a method of making the discrete population of antibodies and which correspond substantially to claims 22-24 of the ‘764 application. Accordingly, no new matter has been added. Applicant requests entry of the Amendment.

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Respectfully submitted,
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SHAWN P. FOLEY Reg. No. 33,071

APPENDICE B- DISCLOSURE DOCUMENT NO.118831 AND TYPED VERSION

Disclosure Document Program
Jul 11, 1983
Pat.&Trademark Off.
Disclosure Document No. 118831

7/10/83-Crystal City-Dr.George Pieczenik

This idea involve generating antibodies to all possible naturally occurring antigenic determinants as well as non naturally or previously occurring antigenic determinants.

Pieczenik patent #4,359,535 allows a method for generating peptides and proteins from random linears of DNA. This allows one to generate all short nucleotide sequences from a DNA molecule that codes for peptide subsections of the various possible proteins. Among this class of peptides exist all possible antigenic determinants based on sequences and local secondary structure.

Monoclonal antibodies formed to this population a la Pieczenik's suggestion to Milstein which became Cotton Milstein exp which became the Kohler Milstein, is then a population of monoclonals to a population of all possible antigenic protein determinants.

These are then sorted into a matrix of monoclonal versus pure antigen such that independent monoclonals to the same antigen is scored (the occurrence of secondary indepents (independents sic) gives one a boundary on the combinatorial options available to the immune system).

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Disclosure Document Program
7/11/83-Crystal City-Dr.George Pieczenik

This matrix of monoclonals versus all small antigen determinants has with in it the possibility of being an active as well as passive method of making a vaccine to any replicating organism, or protein or fused system or protein modified disease causing system.

This matrix can be searched by either the organism causing the disease or an antibody that was created by the disease.

For example, sheared human DNA random as in Pieczenik pat #4,359,535 will generate in expression vector as in ibid all human antigenic determinants that are composed of small polypeptide sequences. Mouse, rat or human or other monoclonals to these antigens in a sorted matrix allow one to probe with human antibody to cross reacting mouse to isolate determinant.

Inversely one can screen with virus, bacterium, protein, nucleic acid , if any reactions compete; Then have identified in matrix monoclonal and specific antigen purified.

Can use viral, plasmid, bacterial, parasite, any organism DNA and generate similar matrix. This allow defining antigenic determinants for these organisms.

Can use spleen, bone marrow, thymus from alternate organism for making different monoclonal matrix.

Idea is to generate matrix of highly specific, pure antibody and antigen to all possible determinants.

APPENDICE C- PROFESSOR NORTON ZINDER AFFIDAVIT AND SUPPORT LETTER FOR PRIORITY, ENABLEMENT AND NOVELTY OF PIECZENIK INVENTION TO MAKE DISPLAY VECTORS FROM FILAMENTOUS BACTERIOPHAGE-

THE ROCKEFELLER UNIVERSITY
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December 21, 2001

To the United States Patent and Trademark Office

1, Norton Zinder, Professor Emeritus at Rockefeller University have directed a genetics laboratory at Rockefeller University for over fifty years . In my laboratory, in 1960, my student Tim Loeb discovered male specific bacteriophages. One of these male specific bacteriophage discovered was f1 bacteriophage. Another male specific bacteriophage was f2 bacteriophage. F2 bacteriophage is a single stranded RNA bacteriophage and was used to decipher the genetic code. F1 is a single stranded DNA phage. This bacteriophage is the f1 bacteriophage described in Dr. Pieczenik's patents 4,359,535, 4,528,266 and 5,866,363 ('363). Dr. Pieczenik filed the 5,866,363 on August 27, 1985. In that original filing and in the issued patent Dr. Pieczenik describes an original method of making, identifying and isolating a surface display vector from f 1 bacteriophage.

On information and belief, the following sections of the original filings and corresponding issued patent are sufficiently explicit descriptions to allow anyone of ordinary skill in the art to have made, identified and isolated a surface display vector from f 1 bacteriophage in 1985.

They are: p. 5 Original 1985 Filing and '363 Column 4 lines 37-42 In preferred embodiments each member of the insert population has a single copy of the sequence of nucleotide triplets, and the insert has between 5 and 7 triplets: the replicating sequence can be a plasmid such as pBR322, a virus, such as lambda-gt 11 or vaccinia, or a filamentous bacteriophage (emphasis added)

P. 7 Original 1985 Filing 'An epitope is a specific site **on the surface of an antigen** that is recognized by an antibody. 363 Column 5 line 43-45 The invention permits the identification of **the specific peptide sequence on a protein that is recognized by an antibody, i.e., the epitope.**
p.13 Original 1985 Filing '363 Column 81ines 56-65 The nucleotide sequence must be inserted at a location in the vector where it will be translated in phase when the vector is transferred into an appropriate host cell, and where it will not interfere with the replication of the vector under the experimental conditions employed, i.e. the nucleotide sequence must be inserted into a non-essential region of the vector. Pieczenik US Patent 4,359,535 and 4,528,266 hereby incorporated by reference, disclose a method for inserting foreign DNA into a non-essential region of a vector.
p.13 Original 1985 Filing '363 Column 9, lines 11-41, 59-67, Column 10 lines 1-23
The nucleotide sequence is advantageously inserted in such a way that the peptide sequence is expressed on the **outside surface of the vector.** To prepare inserts having these characteristics, an appropriate vector, e.g. a phage or plasmid is first selected. The vector is then randomly cleaved according to the method disclosed in Pieczenik, U.S. Patent 4,359,535 and 4,528,266 to yield a population of linear DNA molecules having

circularly permuted sequences. After the cleavage steps, a synthetic oligonucleotide linker bearing a unique nucleotide sequence to both ends of each linearized vector by blunt end ligation. The random linears can then be treated with restriction endonuclease specific to the attached sequences, to generate cohesive ends.

DNA encoding a gene product, eg human hemoglobin, not present in the vector, is fractionated to the desired size eg, fifteen nucleotides long and the nucleotide sequences ligated to the same type of linker used with the random linears. The fractionated nucleotide sequences are then inserted into the random linears and the modified vectors are transferred into appropriate host cells. The host cells are diluted, plated and the individual colonies grown up. On replica plates, the colonies are screened with a monoclonal or polyclonal antibody specific to the gene product.

A positive reaction with the antibody identifies a colony wherein the inserted nucleotide sequence is translated in phase, and the encoded peptide sequence is **on the outside surface** of the polypeptide or protein, **accessible to the antibody screening** assay. If the monoclonal antibody is employed in the screening step, then this procedure will identify only those colonies where the specific peptide sequence comprising the site recognized by that antibody is inserted **on the outside surface of the polypeptide or protein.** If a polyclonal antibody is employed, or a mixture of several monoclonals, then any colony containing on the outside surface of the polypeptide or protein any peptide sequence insert comprising a recognition site of the foreign gene product will be identified. This procedure identifies vectors which can be advantageously used in the present invention.

The procedures given above are and were sufficient for any one of ordinary skill in the art in 1985, such as the members of my laboratory at that time ie Model, Horuichi and Vovis to make and isolate a display phage from f I bacteriophage. It was known at the time that the surface proteins of f I bacteriophage were gene III and gene VIII. That is the sum of the proteins of the bacteriophage itself. Therefore, the procedure above would have necessarily yielded display phage with foreign inserts in gene III and gene VIII.

The reference cited by patent examiner Brusca as prior art (written by my junior staff and postdocs i.e. Horuichi, Vovis and Model show that f 1, M 13 and fd are similar is based on complementation and not sequence all these phage will have similar gene III and gene VIII protein products. However, some differences are important. M13 does not have a Bam site in gene III and therefore makes the Ladner's paper patent claims a bit specious and was one of the reasons that his patents were denied in Europe on enablement. However, our lab bacteriophage f 1 does have a Bam site in gene III which has been used advantageously for making a display phage from f1 bacteriophage.

On information and belief I affirm the above statement to be true.
Prof. Norton Zinder
John D. Rockefeller, Jr. Professor 12/21/01