

The opinion in support of the decision being entered today
is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte ROBERTO CREA

Appeal 2007-2400
Application 10/418,182
Technology Center 1600

Decided: September 21, 2007

Before ERIC GRIMES, LORA M. GREEN, and RICHARD M.
LEBOVITZ, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a library of mutant immunoglobulins. The Examiner has rejected the claims for obviousness and obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

BACKGROUND

Antibodies, or immunoglobulins, include a heavy chain and a light chain, each of which has a constant region and variable region (Specification

5). “Each heavy-chain variable region and each light-chain variable region includes three hypervariable loops, also called complementarity-determining regions (CDRs). The antigen-binding site (Fv) region . . . includes these six hypervariable (CDR) loops.” (*Id.*).

The Specification discloses immunoglobulin mutants made by “walk-through mutagenesis” of immunoglobulin CDRs:

In walk-through mutagenesis a set (library) of immunoglobulins is generated in which a single predetermined amino acid is incorporated at least once into each position of a defined region (or several defined regions) of interest in the immunoglobulin (i.e., into one or more hypervariable loops (CDRs) of the immunoglobulins). The resultant immunoglobulins (referred to herein as “mutated immunoglobulins”) differ from the prototype immunoglobulin, in that they have the single predetermined amino acid incorporated into one or more positions within one or more CDRs of the immunoglobulin, in lieu of the “native” or “wild-type” amino acid.

(*Id.* at 9-10.)

The Specification also discloses libraries of mutant immunoglobulins (referred to as “single predetermined amino acid libraries”) made by performing walk-through mutagenesis on each of the CDRs of an immunoglobulin of interest, alone and in all possible combinations:

Each single predetermined amino acid library contains 64 subset libraries, in which the predetermined amino acid is “walked through” each hypervariable loop (CDR) of the immunoglobulin of interest. . . . The resultant immunoglobulins include mutated immunoglobulins having the predetermined amino acid at one or more positions in each CDR, and collectively having the predetermined amino acid at each position in each CDR. The single predetermined amino acid is “walked through” each of the six hypervariable loops (CDR)

individually; and then through each of the possible combinatorial variations of the CDRs (pairs, triad, tetrads, etc.).

(*Id.* at 15-16.)

The libraries are disclosed to be useful as research tools (*id.* at 17-18).

DISCUSSION

1. CLAIMS

Claims 1-9 are pending and on appeal. The claims have not been argued separately and therefore stand or fall together. 37 C.F.R.

§ 41.37(c)(1)(vii) (2006). Claim 1 is representative and reads as follows:

1. A library for an immunoglobulin of interest, comprising mutated immunoglobulins of interest wherein a single predetermined amino acid has been substituted in at least one position in at least one complementarity-determining region of the immunoglobulin of interest, the library including subset libraries comprising:

- a) a subset library comprising the immunoglobulin of interest,
- b) subset libraries comprising mutated immunoglobulins in which the predetermined amino acid has been substituted in at least one position in one of the six complementarity-determining regions of the immunoglobulin, with one subset library for each of the six complementarity-determining regions, thereby totaling 6 subset libraries;
- c) subset libraries comprising mutated immunoglobulins in which the predetermined amino acid has been substituted in at least one position in two of the six complementarity-determining regions, with one subset library for each of the possible combinations of two of the six complementarity-determining regions, thereby totaling 15 subset libraries;
- d) subset libraries comprising mutated immunoglobulins in which the predetermined amino acid has been substituted in at least one position in three of the six complementarity-determining regions, with one

- subset library for each of the possible combinations of three of the six complementarity-determining regions, thereby totaling 20 subset libraries;
- e) subset libraries comprising mutated immunoglobulins in which the predetermined amino acid has been substituted in at least one position in four of the six complementarity-determining regions, with one subset library for each of the possible combinations of four of the six complementarity-determining regions, thereby totaling 15 subset libraries;
 - f) subset libraries comprising mutated immunoglobulins in which the predetermined amino acid has been substituted in at least one position in five of the six complementarity-determining regions, with one subset library for each of the possible combinations of five of the six complementarity-determining regions, thereby totaling 6 subset libraries; and
 - g) one subset library comprising mutated immunoglobulins in which the predetermined amino acid has been substituted in at least one position in all of the six complementarity-determining regions,

wherein each subset library that contains mutated immunoglobulins, comprises mutated immunoglobulins in which the predetermined amino acid is present at least once at every position in the complementarity-determining region into which the predetermined amino acid has been introduced.

Claim 1 is directed to one of the “single predetermined amino acid libraries” described on pages 15-16 of the Specification. (The Examiner indicated in the Answer that a previous restriction requirement was withdrawn, so “the library comprises all the subsets rather than a single subset.” Answer 3.)

2. REFERENCES

The Examiner relies on the following references:

| | | |
|------|--------------------|---------------|
| Crea | US 5,830,650 | Nov. 3, 1998 |
| Crea | US S.N. 10/371,404 | Feb. 20, 2003 |
| Crea | US 6,649,340 B1 | Nov. 18, 2003 |

Victoria A. Roberts et al., “Antibody Remodeling: A General Solution to the Design of a Metal-Coordination Site in an Antibody Binding Pocket”, 87(17) *Proc. Nat’l Acad. Sci. USA* 6654-6658 (1990).

3. PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-9 stand provisionally rejected for obviousness-type double patenting as being not patentably distinct from claims 32-39 of application 10/371,404 (Answer 4).

Appellant “reserves response on this matter until the time when claims are allowed in the copending application. No terminal disclaimer has been filed at this time.” (Reply Br. 2.)

Since Appellant has provided no basis on which to conclude that the provisional rejection is improper, we affirm it.

4. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-9 stand rejected for obviousness-type double patenting as being not patentably distinct from claim 1 of U.S. Patent 6,649,340 (Answer 4). The Examiner reasons that the instant claims are not patentably distinct from the patented claim “because the broad claimed library having undefined predetermined amino acid encompasses the library of the ‘340 which similarly teaches the subset library wherein the predetermined amino acid is defined” (Answer 4).

As we understand it, the Examiner's reasoning is that the instant library can have any "single predetermined amino acid" substituted for the naturally occurring amino acids in the CDR, while the library claimed in the '340 patent specifies particular amino acids to be substituted for the naturally occurring ones, and therefore the patented library is a subgenus within the instantly claimed genus.

We agree that *if* the library claimed in the '340 patent was a species or subgenus encompassed by the instant claims, a rejection for obviousness-type double patenting would be appropriate. *See Eli Lilly & Co. v. Barr Labs.*, 251 F.3d 955, 971 (Fed. Cir. 2001) ("A patentable distinction does not lie where a later claim is anticipated by an earlier one. . . . "[A] later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim.").

However, we disagree with the Examiner's interpretation of the claims. The instant claim requires numerous subset libraries, which comprise walk-through mutants in one, two, three, four, five, or all six CDRs of an immunoglobulin. The library of the '340 patent's claim 1, by contrast, only requires walk-through mutants in a single CDR. Thus, the library defined by claim 1 of the '340 patent is only one of the many subset libraries required by the instant claims. The '340 patent's library is not a species or subgenus of the instantly claimed library. We reverse the rejection for obviousness-type double patenting based on U.S. Patent 6,649,340.

5. OBVIOUSNESS BASED ON ROBERTS

Claims 1-9 stand rejected under 35 U.S.C. § 103 as obvious in view of Roberts.¹ The Examiner finds that Roberts discloses “an antibody model with mutation at residue 34 (i.e., predetermined amino acid, as claimed) on the first [CDR] of the light chain and residues 89 and 91 on the third [CDR] of the light chain (i.e., predetermined residues in one or more positions in three of the six CDRs, as claimed)” (Answer 7-8). The Examiner concludes:

It would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the total number of subset[s] that can be obtained from the possible combinations of mutations in the CDR regions of a library. The motivation to make such mutations is provided by Crea above in reciting the advantages derived in said mutations e.g., providing a means for systematic insertion of an amino acid into a region of a protein, this method provides a way to enrich a region of a protein with a particular amino acid. . . . Roberts provide[s] similar motivation in the multisite mutations or design of antibodies.

(*Id.* at 8-9.)

Appellant argues that “Roberts et al. focus solely on alteration of certain residues involved in design of a metal-coordination site in an antibody binding pocket, and there is no teaching or suggestion by Roberts et al. to alter any amino acids other than certain specific residues involved in sites for metal coordination” (Br. 8).

¹ The Examiner’s Answer does not actually state which claims are rejected over Roberts. However, the Final Office Action (mailed Dec. 16, 2004) included a rejection of claims 1-9 based on Roberts and the Examiner did not indicate in the Answer that that rejection was withdrawn or modified, so we presume the rejection based on Roberts applies to claims 1-9.

We agree with Appellant that Roberts does not support a prima facie case of obviousness. Roberts teaches a method of “designing cofactor-binding sites for catalytic antibodies” (Roberts, abstract). The disclosed method involves identifying structurally conserved sites within the light chain and heavy chain CDRs and substituting specific amino acids in the CDRs in order to create a zinc-binding site (*id.*).

In other words, Roberts chose a limited number of specific amino acids for substitution, in order to create a three-dimensional arrangement of amino acid side-chains that would coordinate a zinc ion. In the claimed library, by contrast, each amino acid in each of the CDRs is systematically substituted with the same amino acid. The Examiner has not adequately explained why those of skill in the art would have considered it obvious to create the claimed library based on Roberts’ method of limited, deliberate amino acid substitution. The rejection under 35 U.S.C. § 103 based on Roberts is reversed.

6. OBVIOUSNESS BASED ON CREA

Claims 1-9 stand rejected under 35 U.S.C. § 103 as obvious in view of Crea. The Examiner finds that

Crea discloses at col. 11, line 10 that the six hypervariable regions of an Ig, which make up the unique aspect of the antigen binding site, can be mutagenized simultaneously separately within VH or VL chains to study the three dimensional interrelationship of selected amino acid[s] in this site. Crea further discloses at col. 5, line 20 up to col. 6, line 65 that the library used in the method provides a systematic and practical approach for evaluating the importance of particular amino acids, and their position within a defined region of a protein.

(Answer 5.) The Examiner acknowledges that “Crea . . . does not positively recite the total subset of the possible subsets that can be formed from the combined mutations in the CDRs library” (*id.* at 8). However, the Examiner concludes that it would have been obvious

to determine the total number of subset[s] that can be obtained from the possible combinations of mutations in the CDR regions of a library. The motivation to make such mutations is provided by Crea above in reciting the advantages derived in said mutations e.g., providing a means for systematic insertion of an amino acid into a region of a protein, this method provides a way to enrich a region of a protein with a particular amino acid.

(*Id.*)

We agree with the Examiner that the library of claim 1 would have been obvious to a person of ordinary skill in the art based on Crea. Crea teaches the method of walk-through mutagenesis: “[T]he method comprises introducing a predetermined amino acid into each and every position in a predefined region (or several different regions) of the amino acid sequence of a protein. . . . The method can be referred to as ‘walk-through’ mutagenesis.” (Crea, col. 2, ll. 45-65).

Crea teaches that “[u]sually, the region studied will be a functional domain of a protein such as a binding or catalytic domain. For example, the region can be the hypervariable region (complementarity-determining region or CDR) of an immunoglobulin.” (*Id.* at col. 10, ll. 1-5.) Crea also teaches that “several different regions or domains of a protein can be mutagenized simultaneously. The same or a different amino acid can be ‘walked-through’ each region.” (*Id.* at col. 11, ll. 1-3.) Crea specifically suggests that “the six hypervariable regions of an immunoglobulin, which make up

the unique aspects of the antigen binding site (Fv region), can be mutagenized simultaneously, or separately within the V_H or V_L chains, to study the three dimensional interrelationship of selected amino acids in this site” (*id.* at col. 11, ll. 10-15.)

Crea provides an “Illustration[] of Walk-through Mutagenesis” (col. 12, l. 55) in which “five out of six CDRs of the MCPC 603 Fv molecule is performed VL CDR2 was not targeted for mutagenesis because structural studies indicated that this region contributes little to the binding site in MCPC 603” (*id.* at col. 19, ll. 29-40).

We agree with the Examiner that Crea’s teachings would have suggested the claimed library to those of ordinary skill in the art. Crea teaches walk-through mutagenesis of immunoglobulin CDRs. Crea also teaches that “*the same* or different” amino acid can be walked-through each region and that the CDRs “can be mutagenized simultaneously, or separately within the V_H or V_L chains.” Thus, Crea would have suggested, to the skilled artisan, making a library containing the starting immunoglobulin and all of the possible CDR walk-through mutants of that immunoglobulin; i.e., mutants created by carrying out walk-through mutagenesis of (a) each CDR individually, (b) each of the possible pairs, trios, quartets, and quintets of CDRs mutagenized simultaneously, and (c) all six CDRs mutagenized simultaneously – in other words, the library defined by instant claim 1.

Crea teaches that walk-through mutagenesis

can be used to generate libraries of mutant proteins which are of a practical size for screening. The method can be used to study the role of specific amino acids in protein structure and function and to develop new or improved proteins and polypeptides such

as enzymes, antibodies, binding fragments or analogues thereof, single chain antibodies and catalytic antibodies.

(*Id.* at col. 3, ll. 33-39.) Thus, those skilled in the art would have expected that the library suggested by Crea would have been useful as a research tool.

Appellant argues that the Examiner erred in interpreting the claims to encompass a library in which different amino acids are substituted into CDRs (Br. 7). We agree with Appellant that the claims, when read in light of the Specification, are properly interpreted as limited to a library in which the *same* “single predetermined amino acid” has been substituted into different CDRs of an immunoglobulin. The Examiner’s error is harmless, however, since Crea specifically suggests “*the same* or different amino acid” in different regions of a protein, including the CDRs of an immunoglobulin (see Crea, col. 11, ll. 1-15).

Appellant also argues that it would not have been obvious, given the teachings of the '650 Patent, to generate all of the specific subset libraries for the specific, different combinations of the complementarity-determining regions, as required by the claims of the invention. Although the '650 patent indicates that the six hypervariable regions of an immunoglobulin can be mutagenized simultaneously or separately (see col. 11, line 10 et seq.), it does not teach or suggest that libraries having the specific combinations of permutations of the claimed invention should be prepared.

(Reply Brief, page 3.)

We disagree. It is true that Crea does not expressly suggest making each of the libraries recited in instant claim 1, but the prior art need not expressly suggest an invention in order to have made it obvious. “[T]he ‘motivation-suggestion-teaching’ test asks not merely what the references disclose, but whether a person of ordinary skill in the art, possessed with the

understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims.” *In re Kahn*, 441 F. 3d 977, 988 (Fed. Cir. 2006). *See also KSR Int’l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) (The obviousness analysis “can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.”); *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (Fed. Cir. 2006) (The “suggestion test is in actuality quite flexible and not only permits, but *requires*, consideration of common knowledge and common sense.”).

Here, the library defined by claim 1 represents the product of taking the process disclosed by Crea to its logical conclusion by carrying out walk-through mutagenesis of an immunoglobulin’s CDRs individually and in all possible combinations. The nature of the problem addressed by Crea would have suggested to the skilled artisan that the more complete the library of walk-through mutants, the more useful it would be as a research tool. We agree with the Examiner that a person of ordinary skill in the art would have considered it obvious, based on Crea’s teachings, to make such a library. The rejection of claims 1-9 under 35 U.S.C. § 103 based on Crea is affirmed.

SUMMARY

We reverse the rejection for obviousness-type double patenting based on U.S. Patent 6,649,340 and the rejection under 35 U.S.C. § 103 based on Roberts. However, we affirm the provisional rejection for obviousness-type double patenting and the rejection under 35 U.S.C. § 103 based on Crea.

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No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc:

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