composite heavy chain, amino acid residues 5, 8, 10, 12 to 17, 19, 21, 22, 40, 42 to 44, 66, 68, 70, 74, 77, 79, 81, 83 to 85, 90, 92, 105, 109, 111 and 113 at least are acceptor residues and amino acid residues 23, 24, 31 to 35, 49 to 58 and 95 to 102 at least are donor residues.

4. An anti-CD3 antibody molecule having affinity for the CD3 antigen comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain comprising acceptor antibody heavy chain framework residues and donor antibody heavy chain antigen-binding residues, said donor antibody having affinity for said CD3 antigen, wherein, according to the Kabat numbering system, in said composite heavy chain, amino acid residues 5, 8, 10, 12 to 17, 19, 21, 22, 40, 42 to 44, 66, 68, 70, 74, 77, 79, 81, 83 to 85, 90, 92, 105, 109, 111 and 113 at least are acceptor residues and amino acid residues 23, 24, 31 to 35, 49 to 58 and 95 to 102 at least are donor residues.

5. An anti-CD4 antibody molecule having affinity for the CD4 antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain comprising acceptor antibody heavy chain framework residues and donor antibody heavy chain antigen-binding residues, said donor antibody having affinity for said CD4 antigen, wherein, according to the Kabat numbering system, in said composite heavy chain, amino acid residues 5, 8, 10, 12 to 17, 19, 21, 22, 40, 42 to 44, 66, 68, 70, 74, 77, 79, 81, 83 to 85, 90, 92, 105, 109, 111 and 113 at least are acceptor residues and amino acid residues 23, 24, 31 to 35, 49 to 58 and 95 to 102 at least are donor residues.

6. An anti-adhesion molecule antibody molecule having affinity for an adhesion molecule and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain comprising human

acceptor antibody heavy chain framework residues and donor antibody heavy chain antigen-binding residues, said donor antibody having affinity for said adhesion molecule wherein, according to the Kabat numbering system, in said composite heavy chain, amino acid residues 5, 8, 10, 12 to 17, 19, 21, 22, 40, 42 to 44, 66, 68, 70, 74, 77, 79, 81, 83 to 85, 90, 92, 105, 109, 111 and 113 at least are acceptor residues and amino acid residues 23, 24, 31 to 35, 49 to 58 and 95 to 102 at least are donor residues.

7. The antibody molecule of any one of claims 2 to 6 wherein amino acid residues 71, 73 and 78 in said composite heavy chain are additionally donor residues.

8. The antibody molecule of any one of claims 1 to 7, wherein amino acid residues 26 to 30 and 59 to 65 in said composite heavy chain are additionally donor residues.

9. The antibody molecule of any one of claims 1 to 8, wherein at least one of amino acid residues 1, 3, and 76 in said composite heavy chain are additionally donor residues.

10. The antibody molecule of any one of claims 1 to 9, wherein at least one of amino acid residues 36, 94, 104, 106 and 107 in said composite heavy chain are additionally donor residues.

11. The antibody molecule of claim 10, wherein at least one of amino acid residues 2, 4, 6, 38, 48, 67 and 69 in said composite heavy chain are additionally donor residues.

12. The antibody molecule of any one of claims 1 to 11 wherein amino acid residues 7, 9, 11, 18, 20, 25, 37, 39, 41, 45, 47, 48, 72, 75, 80, 82, 86 to 89, 91, 93, 103, 108, 110 and 112 in said composite heavy chain are additionally acceptor residues.

13. The antibody molecule of any one of claims 1 to 12,

wherein said complementary light chain is a composite light chain having a variable domain comprising acceptor antibody light chain framework residues and donor antibody light chain antigen-binding residues, said donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite light chain, amino acid residues 5, 7 to 9, 11, 13 to 18, 20, 22, 23, 39, 41 to 43, 57, 59, 61, 72, 74 to 79, 81, 82, 84, 86, 88, 100, 104, 106 and 107 at least are acceptor residues and amino acid residues 24 to 34, 46, 48, 50 to 56, 58, 71 and 89 to 97 at least are donor residues.

14. The antibody molecule of claim 13, wherein amino acid residues 1, 3 and 47 in said composite light chain are additionally donor residues.

15. The antibody molecule of claim 13 or claim 14, wherein amino acid residues 36, 44, 47, 85 and 87 in said composite light chain are additionally donor residues.

16. The antibody molecule of any one of claims 13 to 15, wherein at least one of amino acid residues 2, 4, 6, 49, 62, 64 to 69, 98, 99, 101 and 102 in said composite lightly chain are additionally donor residues.

17. The antibody molecule of any one of claims 13 to 16, wherein at least one of amino acid residues 1, 3, 10, 12, 21, 40, 60, 63, 70, 73, 80, 103 and 105 in said composite light chain are additionally donor residues.

18. A therapeutic or diagnostic composition comprising the antibody molecule of any one of claims 1 to 17 in combination with a pharmaceutically acceptable carrier, diluent or excipient.

19. A method for producing a recombinant antigen binding molecule having affinity for a predetermined antigen comprising the steps of:

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[1] determining the amino acid sequence of the variable domain of the heavy chain of a donor antibody which has affinity for said predetermined antigen;

[2] determining the amino acid sequence of the variable domain of the heavy chain of a non-specific acceptor antibody;

[3] providing a composite heavy chain for an antibody molecule, said composite heavy chain having acceptor framework residues and donor antigen binding residues wherein, according to the Kabat numbering system, amino acid residues 5, 8, 10, 12 to 17, 19, 21, 22, 40, 42 to 44, 66, 68, 70, 74, 77, 79, 81, 83 to 85, 90, 92, 105, 109, 111 and 113 at least are acceptor residues and amino acid residues 23, 24, 31 to 35, 49 to 58 and 95 to 102 at least are donor residues;

[4] associating the heavy chain produced in step [3] with a complementary light chain to form an antibody molecule;

[5] determining the affinity of the antibody molecule formed in step [4] for said predetermined antigen;

[6] if the affinity determined in step [5] is not equivalent to that of the donor antibody, providing a heavy chain as described in [3] above but in which amino acid residues 71, 73 and 78 are additionally donor residues;

[7] associating the heavy chain produced in step [6] with a complementary light chain to form an antibody molecule;

[8] determining the affinity of the antibody molecule formed in step [7] for said predetermined antigen;

[9] if the affinity determined in step [8] is not equivalent to that of the donor antibody, providing a heavy chain as described in [6] above but in which amino acid residues 26 to 30 are additionally donor residues;

[10] associating the heavy chain produced in step [9] with a complementary light chain to form an antibody molecule;

[11] determining the affinity of the antibody molecule formed in step [10] for said predetermined antigen;

[12] if the affinity determined in step [11] is not equivalent to that of the donor antibody, providing a heavy chain as described in [9] above but in which at least one of amino acid residues 1, 3, and 76 are additionally donor residues;

[13] associating the heavy chain produced in step [12] with a complementary light chain to form an antibody molecule;

[14] determining the affinity of the antibody molecule formed in step [13] for said predetermined antigen;

[15] if the affinity determined in step [14] is not equivalent to that of the donor antibody, providing a heavy chain as described in [12] above but in which at least one of amino acid residues 36, 94, 104, 106, 107 are additionally donor residues;

[16] associating the heavy chain produced in step [15] with a complementary light chain to form an antibody molecule.

[17] determining the affinity of the antibody molecule formed in step [16] for said predetermined antigen;

[18] if the affinity determined in step [17] is not equivalent to that of the donor antibody, providing a heavy chain as described in [15] above but in which at least one of amino acid residues 2, 4, 6, 38, 48, 67 and 69 are additionally donor residues; and

[19] associating the heavy chain produced in step [18] with a complementary light chain to form an antibody molecule.

20. The method of claim 19, further comprising the steps of:

[1] determining the amino acid sequence of the variable domain of the light chain of said donor antibody which has affinity for said predetermined antigen;

[2] determining the amino acid sequence of the variable domain of the light chain of a non-specific acceptor antibody;

[3] providing a composite light chain for an

antibody molecule, said composite light chain having acceptor framework residues and donor antigen binding residues wherein, according to the Kabat numbering system, amino acid residues 5, 7 to 9, 11, 13 to 18, 20, 22, 23, 39, 41 to 43, 57, 59, 61, 72, 74 to 79 to 79, 81, 82, 84, 86, 88, 100, 104 and 106 to 109 at least are acceptor residues and amino acid residues 24 to 34, 46, 48, 50 to 56, 58, 71 and 89 to 97 at least are donor residues;

[4] associating the light chain produced in step [3] with a complementary heavy chain to form an antibody molecule;

[5] determining the affinity of the antibody molecule formed in step [4] for said predetermined antigen;

[6] if the affinity determined in step [5] is not equivalent to that of the donor antibody, providing a light chain as described in [3] above but in which amino acid residues 1, 2, 3 and 47 are additionally donor residues;

[7] associating the light chain produced in step [6] with a complementary heavy chain to form an antigen-binding molecule;

[8] determining the affinity of the antigen-binding molecule formed in step [7] for said predetermined antigen;

[9] if the affinity determined in step [8] is not equivalent to that of the donor antibody, providing a light chain as described in [6] above but in which amino acid residues 36, 44, 47, 85 and 87 are additionally donor residues;

[10] associating the light chain produced in step [9] with a complementary heavy chain to form an antibody molecule;

[11] determining the affinity of the antibody molecule formed in step [10] for said predetermined antigen;

[12] if the affinity determined in step [11] is not equivalent to that of the donor antibody, providing a light chain as described in [9] above but in which at least one of amino acid residues 2, 4, 6, 49, 62, 64 to 69, 98, 99, 101 are additionally donor residues; and

[13] associating the light chain produced in step [9]

with a complementary heavy chain to form an antibody molecule.

DOCKET NO.: CARP 0000X PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

John R. Adair, et al.

Serial No.: 07/743,329 Group Art Unit: 1807

Filed: September 17, 1991 Examiner: L. Bennett

For: HUMANISED ANTIBODIES

I, Doreen Yatko Trujillo, Registration No. 35,719 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

On February 7, 1994

Doreen Yatko Trujillo

Doreen Yatko Trujillo, Reg. No. 35,719

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

AMENDMENT

This amendment is filed in response to the Office Action mailed September 7, 1993. A petition for extension of time and the appropriate fee is attached.

In the claims:

Please cancel claims 73 to 107, 109 to 113 and 115 to 119, without prejudice.

Carter Exhibit 2010
Carter v. Adair
Interference No. 105,744

Please amend claims 67 and 71 as follows:

67. (Amended) An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain comprising human acceptor antibody heavy chain [framework] residues and donor antibody heavy chain [antigen-binding] residues, said donor antibody having affinity for said predetermined antigen, said variable domain further comprising complementarity determining regions, wherein, according to the Kabat numbering system, in said composite heavy chain, said complementarity determining regions comprise donor residues at least at residues 31 to 35, 50 to 58 and 95 to 102; amino acid residues 5, 8, 10, 12 to 17, 19, 21, 22, 40, 42 to 44, 66, 68, 70, 74, 77, 79, 81, 83 to 85, 90, 92, 105, 109, 111 and 113 at least are acceptor residues; and amino acid residues 23, 24, [31 to 35,] 49 [to 58], 71, 73[,] and 78 [and 95 to 102] at least are donor residues.

Claim 71, line 2, please delete "48" and insert --46--.

REMARKS

Claims 67-72, 108 and 114 are pending. The number of claims pending in the present application has been reduced in order to expedite the prosecution of the case. The deletion of some claims should not be taken to be an admission that the subject

matter of the deleted claims is unpatentable. The Applicants reserve the right to file continuation applications directed to the deleted subject matter. The Examiner is thanked for bringing the typographical error in Claim 71 to the Applicants' attention.

To the extent the rejections are maintained against amended claim 67, and the remaining claims, Applicants respectfully request reconsideration for the reasons set forth below.

Rejections Under 35 U.S.C. § 112, First Paragraph

In paragraph 16 of the present Office Action, the Examiner contends that the application does not contain any support for the recitation of acceptor residues in the light or heavy chains. It is submitted, for the following reasons, that the Examiner's contention is incorrect.

At a very helpful interview held at the beginning of 1993, there was some discussion of the word "comprising" as used in the claims under consideration at that time. In those claims, it was only specified that certain residues should be donor residues. It was considered that it was not clear whether these were the only residues which could be donor residues. The alternative view was that these were only the minimum number of residues which must be donor but that any of the other residues could also be donor.

If the second line of interpretation were taken, the claims could be read to cover a situation in which all except one of the residues in the variable domain were donor residues. In

this case, the claims could then be interpreted to cover a structure similar to a "chimeric" antibody comprising a donor variable domain and a human constant region. Such chimeric antibodies were already well known at the priority date.

It plainly is not the intention of the Applicants to claim chimeric antibodies or any similar structures. As can be seen from the description, the superhumanised antibodies of the present invention are compared to the prior art chimeric antibodies. Moreover, the present invention was intended to deal with the problem of chimeric antibodies in that chimeric antibodies were believed to be too "foreign" because of the presence of the complete donor variable domain.

For the above reasons, it is clear that the wording of the claims needed to be changed so that the Applicants' intention of excluding chimeric antibodies was made effective. The language now present in the claims puts this intention clearly into effect.

As to support for this wording, the Examiner is referred firstly to page 16, under the heading "Protocol". It can be seen from this paragraph that the first step in the process involves the choice of an appropriate acceptor chain variable domain. This acceptor domain must be of known sequence. Thus, the protocol starts with a variable domain in which all the residues are acceptor residues. In the sentence bridging pages 16 and 17, it is stated that:

> "The CDR-grafted chain is then designed starting from the basis of the acceptor sequence".

On page 17, in the middle paragraph, it is stated that:

> "The positions at which donor residues are to be substituted for acceptor in the framework are then chosen as follows...."

This again shows that, unless a residue is chosen for substitution, it will remain as in the acceptor sequence.

It must also be borne in mind that the purpose of the invention is to obviate some of the disadvantages of prior art proposals. The proposal of using chimeric antibodies had the disadvantage that they were more "foreign" than desirable. The problem of making CDR-grafted antibodies was that they generally did not provide good recovery of affinity. Thus, the aim of the present invention was to minimise as far as possible the "foreign" nature of the antibody while maximising as far as possible its affinity.

Bearing the passages referred to above and the aim of the invention in mind, it would have been abundantly clear to the skilled person reading the application that as many residues as possible should remain as acceptor residues. If this were not the case, it could hardly be said that the composite chain is based on the acceptor sequence.

The skilled person reading the application can plainly see that certain residues have been considered for changing from acceptor to donor. These are clearly set out in the description.

It would be plain to the skilled person that all other residues should not be considered for changing at all. It would therefore be obvious that any residue which is not specified as being under consideration for changing must remain as in the acceptor chain.

It may be that there is no explicit statement in the description that the specified residues should remain as in the acceptor chain. However, the disclosure in a specification is not limited to the explicit disclosure but also includes that which is implicit. It is implicit, in the recitation that the chain is based on the acceptor and that only certain residues are considered for changing, that all non-specified residues must remain as acceptor residues. Subject matter which might be fairly deduced from the disclosure is not new matter. *Acme Highway Products Corp. v. D.S. Brown Co.*, 431 F.2d 1074, 1080, 167 U.S.P.Q. 129, 132-133 (6th Cir. 1970), *cert denied*, 401 U.S. 956 (1971).

Another way to look at it is to consider a different way in which the claim could be drafted. It could be specified that in the composite chain, at least a certain minimum number of residues are donor residues (as in the present claims) and at most a certain maximum number of residues are donor residues. The maximum number would be derived by listing all the residues which are considered for changing. Such an amendment would have clear explicit basis in the description because all those residues are mentioned as such. However, the effect of such an amendment would be to produce claims of exactly the same scope as the present claims. It can thus be

seen that the present claims do not add subject matter but are plainly properly based on the disclosure in the description.

It is therefore submitted that the claims are fully supported by the description, are commensurate in scope with the disclosure in the description, and are properly delimited over the prior art.

The rejections of Claims 73-107, 109-113, and 115-119 under 35 U.S.C. §112 has been rendered moot by their withdrawal.

In paragraph 26 of the Office Action, the Examiner maintains the rejection of the claims for lack of enablement. It is submitted that this rejection cannot stand for the following reasons.

The Examiner contends that the description does not provide a "representative" number of Examples falling within the scope of the claims. Even if this were the case (and it is not, for reasons set out below) this does not provide a proper basis for rejection under 35 U.S.S. §112. A "representative" number of Examples is not required to obtain a patent. All that is required is that the disclosure be enabling. Enablement does not depend on the number of examples provided. Sufficient disclosure can be provided by illustrative examples or terminology. Further, "It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991).

The Examiner also appears to be arguing that it may be that some antibodies will not be susceptible to the protocol of the present invention, i.e. that not all embodiments will work. Even if this were the case (and it is not, for reasons set out below). this also does not provide a proper basis for rejection under 35 U.S.C. §112. That inoperative embodiments may be encompassed is not detrimental. "It is not the function of claims or the specification to exclude all inoperative substances." *Ex parte Janin,* 209 U.S.P.Q. 761, 763 (Bd. of App. 1979). "The mere fact that a claim embraces undisclosed or inoperative species or embodiments does not necessarily render it unduly broad." *Horton v. Stevens,* 7 U.S.P.Q.2d 1245, 1247 (Bd. of Pat. App. & Int. 1988).

Apart from the legal points made above, it is submitted that the Examiner is incorrect on the technical facts. Before expanding on this, however, it would be worthwhile to make a few points concerning affinity. There is no absolute value which can be set which defines good affinity. Affinity can be measured, for instance in reciprocal moles (M^{-1}). In this measurement system, affinity can vary from 10^6 to 10^{12}.

Natural antibodies, as produced *in vivo,* do not all have the same affinity, even for the same antigen. Thus, in the normal polyclonal antiserum produced on challenge by an antigen, the body will produce a variety of antibodies having affinities within the range given above. Monoclonal antibodies, as produced by hybridoma

technology, also have varying affinities, again within the range given above. The variation in the affinity may in part be due to the structure of the antibody and in part to the structure of the antigen. It may therefore be that a good antibody directed against antigen X has an affinity of only 10^7 whereas a good antibody against antigen Y may have an affinity of 10^{12}. These are both good antibodies, even though they have very different affinities.

It can be seen that if an engineered antibody is produced against antigen X with an affinity of 10^8, this will be regarded as being exceptional, in that the affinity has gone up 10 fold compared to the good antibody. However, if an engineered antibody recognizing antigen Y is produced with an affinity of 10^8, this will be regarded as being an awful result as the affinity will have been reduced 10,000 fold.

Thus, the only sensible way to determine whether an engineered antibody is successful is to compare its affinity with that of the prototype antibody from which it is derived. It is pointless to look at the absolute value of the affinity because this does not tell you anything about the success or failure of the engineering operation. It is for this reason that the Applicants have provided such qualitative evidence of the success of the protocol described in the application.

Further, in some cases, a residue which is selected for changing according to the protocol described in the application may

not need to be changed. It may be that, fortuitously, it is the same in the donor and acceptor chains. This does not mean that, if the residues had been different, it would not have been changed. It merely means that, in effect, the change had already been made.

As to the number of antibodies which have been shown to have been successfully superhumanised using the protocol of the present invention, the Examiner is requested to look at the sheets attached to the previous response submitted April 7, 1993. Although Applicants are not required to provide a "representative number of examples", the provision of so many antibodies in these attachments should have satisfied any doubts on the part of the Examiner. Yet the Examiner makes no reference to these attachments and the evidence they provide.

The Examiner is also referred to the passage beginning on page 17 through page 19 of the last response. This shows in detail that a representative number of antibodies falling within the terms of the present claims were superhumanised successfully. Again the Examiner has not even referred to these pages. The Examiner has not provided any reasoning as to why these pages are not persuasive. It is submitted that mere allegation is not enough. The Examiner must also provide references or, if based upon personal knowledge, an affidavit, in support of the Examiner's allegations. MPEP § 706.02.

As has been shown by the third sheet attached to the previous response, the successful antibodies are representative not

only in number, but also as regards to antigens recognized. The antigens include cell surface antigens found on both healthy and cancerous cells, soluble cytokines and adhesion molecules. These are all very different in structure and function, yet antibodies against each of them have been successfully superhumanised using the protocol of the present invention.

It is no doubt the case that some of the antibodies referred to in the sheets were more successfully humanised than others. However, the reasons for this were clearly set out in the previous response. Thus, evidence that the replacement scheme is not generally applicable has not been provided.

The Examiner places much reliance on the prior art as, in her view, showing that there would have been no reasonable expectation of success. The Applicants agree that, if there were only the prior art to go on, then there would have been no reasonable expectation of success. However, the skilled person trying to put the present invention into practice does not have to rely on only the prior art. The skilled person has available the teaching of the present application. It is specifically stated in the application that the present protocol represents a departure from the procedures of Reichmann and Queen, at least. Thus, the skilled person would not rely on Reichmann and Queen as teachings relevant to whether the present description is enabling.

It is submitted that the skilled person would rely on the clear teaching given in the application and find that it is

enabling. The specification plainly sets out what actions need to be taken. It is presumed that the Examiner agrees that the skilled person could have taken those actions. The application also sets out that, contrary to the teachings of Reichmann and Queen, the protocol is generally applicable. The application further shows that it had been successfully implemented. Thus, it is submitted that the skilled person would find that the present application is properly enabled the full extent of the claims.

Rejections Under 35 U.S.C. § 103

The Examiner rejected all the claims as being obvious over Reichmann and Queen. However, this rejection appears contrary to her previous assertions. When attacking the enablement of the claims, the Examiner stated that:

> "... in light of the prior art (for instance, Reichmann et al., Queen et al., and Chothia et al.) such a universal property appears to be unpredictable... The prior art does not teach that standardized principle... is possible."

(emphasis added)

The Applicants agree with the Examiner that the prior art provides no predictability of success and certainly no expectation that a generally applicable principle can be devised. It is submitted that this is a clear indication that the surprising

discovery that there is a generally applicable principle involves an invention.

The Examiner indicated that the arguments previously presented by the Applicants were deemed to be non-persuasive because they did not address the combined effect of Reichmann and Queen. This, of course, assumes that the skilled artisan would have combined Reichmann and Queen in the first place. The Examiner has shown no reason why Reichmann and Queen would have been combined. It is submitted that there is no reason why they should be combined.

The earlier publication is Reichmann. This shows a relatively simple procedure in which the six CDRs from a rat antibody against a leukocyte cell surface antigen are transferred onto human frameworks. The only additional residue change is in the heavy chain at residue 27. The reason that this residue is changed is because it was atypical in the human (acceptor) chain. The change was to replace residue 27 with the more normal acceptor residue. Thus, the teaching of Reichmann is that, as long as you have normal human (acceptor) chain, all that is needed is for the CDRs to be changed.

Queen does in fact refer to Reichmann. Reichmann is reference 24 in Queen. However, this is only referred to in passing on page 10029 as being an example of the work of Winter and his colleagues. The teaching of Queen clearly goes beyond that of

Reichmann. Thus, there is no incentive to try to combine the teachings of Reichmann and Queen.

Even if one could find some motivation for combining Reichmann and Queen, it is submitted that Reichmann would not add to Queen such that Applicants invention would be rendered obvious. Reichmann teaches the skilled person to use a normal acceptor sequence and merely to change the CDRs. If the acceptor sequence is not normal, then the abnormal residues are to be changed to normal acceptor residues. This is all disclosed in Queen. Since, at best, Queen incorporates all the teaching of Reichmann, even if Reichmann and Queen are combined, the total teaching is no more than teaching of Queen by itself. If the Examiner is of the contrary view, she is requested to point out specifically the teaching in Reichmann which is not present in Queen and why she believes this additional teaching, when combined with the teaching in Queen, renders the present claims obvious.

For the reasons set forth in the previous response, it is submitted that Queen, and therefore also a combination of Queen and Reichmann, does not render the present claims obvious.

The Examiner noted that the previously presented arguments concentrated on the process aspects of the disclosure in Queen and contended that this is irrelevant as far as the product claims in the present application are concerned. It is submitted that this is not correct. The only specifically disclosed product in Queen does not fall within the terms of the present claims. It

is therefore necessary for the Examiner to show that a product falling within the terms of the claims would have been produced using the teachings of Queen, alone or in combination with the prior art, or obvious variants thereof. If there is no expectation that such a product would have been produced, then the product claims are not obvious.

To maintain otherwise is to employ impermissible hindsight. Queen only describes the replacement of some acceptor residues outside the CDR for a "specific" antibody. Queen does not disclose, or even suggest, a "general" approach for replacing acceptor residues outside the CDRs with donor residues. In fact, the absence of such disclosure in Queen, or in any of the prior art cited, was previously emphasized in the Examiner's rejection under § 112 for enablement. Therefore, it is respectfully submitted that the Examiner would not have even contemplated that Queen discloses, or suggests, a general superhumanised antibody as claimed without the benefit of Applicants' disclosure. Neither would one skilled in the art.

Further, it is submitted that the Examiner has not established a *prima facie* case of obviousness. The teachings from the prior art *itself* should appear to have suggested the claimed subject matter to a person of ordinary skill in the art to establish a *prima facie* case. *In re Rijckaert*, 28 U.S.P.Q. 2d 1955 (Fed. Cir. 1993). As already admitted by the Examiner in the rejections under § 112, the expectation that a generalized approach

is feasible is nowhere present in the prior art. Thus, the claims as drafted, covering superhumanised antibodies in general (i.e., not limited to a particular antibody) are not obvious over the prior art.

The Examiner also asserts that how the residues are identified is irrelevant. It is submitted that this is not the case when the rejection is one for obviousness. The references do not disclose the residues claimed by Applicants. To render Applicants' claims obvious, the Examiner needs to show that the prior art could lead one skilled in the art to identify the same residues as are identified in the present claims. The Examiner has not shown any reason why the skilled person, carrying out the method described by Queen, alone or in combination with Reichmann, would have expected to identify the specific sets of residues identified in the present claims. In this regard, it is noted that a rejection for obviousness was not levied against the method claims in the Office Action--i.e., claims 118 and 119.

It is again to be pointed out that the present claims cannot be generalized to "an antibody in which the CDRs and some, (unspecified) framework residues have been changed." The present claims relate to "an antibody in which the CDRs and only certain, specific framework residues have been changed." Nothing in the prior art, whatever combination is used, leads the skilled person to the specific set of residues set forth in the present claims.

It is therefore submitted that the present claims are not at all obvious over Queen, combined with Reichmann, or on its own.

Paragraphs 18 to 25 and 27 to 29

The contents of paragraphs 18 to 25 and 27 to 29 are noted with appreciation.

The foregoing represents a bona fide attempt to advance the case to allowance. Applicants respectfully request that all presently pending claims be allowed.

Respectfully submitted,

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different paths, and by ensuring that an azimuthally uniform coverage of stations is used in the averaging calculation. To compensate for other factors, such as focal depth, fault geometry and corner frequency would require such a detailed knowledge of the earthquake source that the M_s measurement itself would be redundant.

The results of this analysis can be summarized in five points.

(1) A global average moment–magnitude relationship M_s has been defined which can be used to predict M_0 over a wide range of magnitudes and scalar moments.

(2) The variance of surface wave measurements for an event of a particular scalar moment is ~0.2 magnitude units.

(3) Large regional biases in M_s exist.

(4) Differences in source scaling may explain some of the differences. Specifically, observations show that the transition from a slope of unity to a smaller value occurs at large moments for continental events than for ridge and fracture zone events, suggesting systematic differences in stress drop.

(5) Other systematic factors affecting the calculation of M_s also appear to contribute to the observed regional bias.

We thank Professor J. H. Woodhouse for reading and correcting the manuscript and Professor H. Kanamori for constructive criticism throughout our work on this subject. This work was supported by the NSF.

Received 20 October 1987; accepted 4 February 1988.

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Reshaping human antibodies for therapy

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A human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hypervariable regions from the heavy- and light-chain variable domains of a rat antibody directed against human lymphocytes. The reshaped human antibody is as effective as the rat antibody in complement and is more effective in cell-mediated lysis of human lymphocytes.

In 1890 it was shown that resistance to diphtheria toxin could be transferred from one animal to another by the transfer of serum. It was concluded that the immune serum contained an anti-toxin, later called an antibody[1]. For many years animal antisera were used in the treatment of microbial infections and for the neutralization of toxins in man[2]. More recently rodent monoclonal antibodies (mAbs)[3] have been used as 'magic bullets'[4] to kill and to image tumours[5,6]. The foreign immunoglobulin, however, can elicit an anti-globulin response which may interefere with therapy[7] or cause allergic or immune complex hypersensitivity[8]. Thus ideally human antibodies would be used. Human immunoglobulins are widely used as both prophylactic and microbicidal agents[9], but it would be far better to have available human mAbs of the desired specificity. It has proven difficult, however, to make such mAbs by the conventional route of immortalization of human antibody-producing cells[9].

There is an alternative approach. Antibody genes have been transfected into lymphoid cells, and the encoded antibodies expressed and secreted; by shuffling genomic exons, simple chimaeric antibodies with mouse variable regions and human constant regions have been made[10–12]. Such chimaeric antibodies have at least two advantages over mouse antibodies. First, the effector functions can be selected or tailored as desired. For example, of the human IgG isotypes, IgG1 and IgG3 appear to be the most effective for complement and cell-mediated lysis[13–15], and therefore for killing tumour cells. Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy[16,17] by avoiding anti-isotypic antibodies. The extent to which anti-idiotypic responses to rodent antibodies in therapy are dictated by foreign components of the variable versus the constant region is not known, but the use of human isotypes should reduce the anti-idiotypic response. For example, when mice were made tolerant to rat immunoglobulin constant-region determinants, administration of rat anti-lymphocyte antibodies did evoke anti-idiotypic responses, but these were delayed and weaker than in animals that had not been made tolerant[18]. Nevertheless, it is likely that a chimaeric antibody would provoke a greater immune response than a human mAb.

We have attempted to build rodent antigen binding sites directly into human antibodies by transplanting only the antigen binding site, rather than the entire variable domain, from a rodent antibody. The antigen binding site is essentially encoded by the hypervariable loops at one end of the β-sheet framework. The hypervariable regions of the heavy chain of mouse antibodies against a hapten[19] or a protein antigen[20] were previously transplanted into a human heavy chain, and, in association with the mouse light chain, the antigen binding site was retained.

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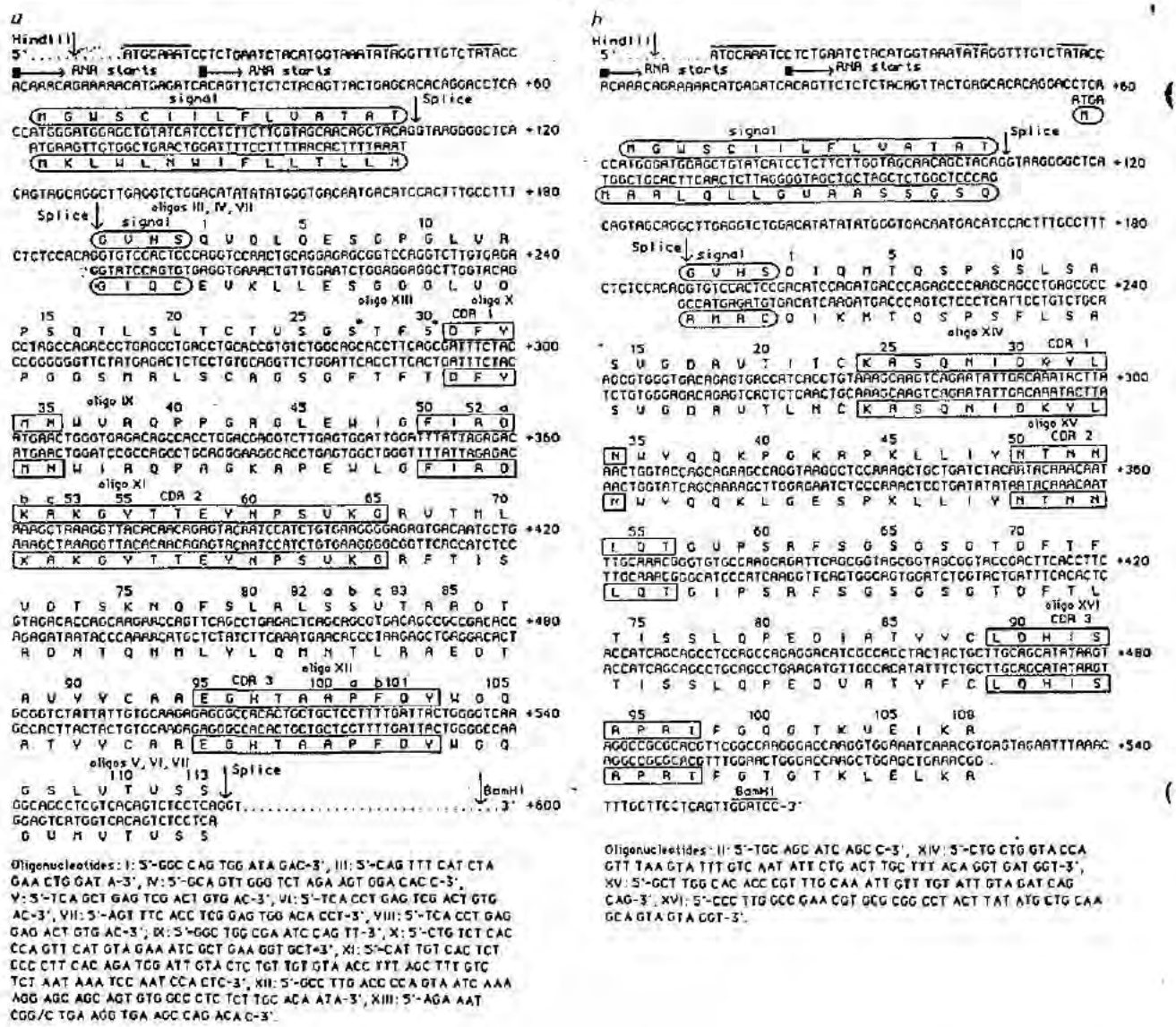

Fig. 1 Heavy-chain (*a*) and light-chain (*b*) sequences of the variable domains of reshaped (upper line) or rat YTH 34.5HL (lower line) antibodies. The reshaped heavy-chain variable domain HuVHCAMP was based on the HuVHNP gene[12,19], with the framework regions of human NEW (see note) alternating with the hypervariable regions of rat YTH 34.5HL. The reshaped light-chain variable domain HuVLCAMP is a similar construct, except with the framework regions of the human myeloma protein REI, with the C-terminal and the 3' non-coding sequence taken from a human J_κ-region sequence[36]. The sequences of oligonucleotide primers are given and their locations on the genes are marked.

Methods. Messenger mRNA was purified[37] from the hybridoma clone YTH 34.5HL ($\gamma 2a, \kappa^a$). First strand cDNA was synthesized by priming with oligonucleotides complementary to the 5' end of the CH1 (oligonucleotide II) and the $C\kappa$ exons (oligonucleotide IX), and then cloned and sequenced as described previously[38,39]. Two restriction sites (*Xba*I and *Sal*I) were introduced at each end of the rat heavy-chain variable region RaVHCAMP cDNA clone in M13 using mutagenic oligonucleotides III and V respectively, and the *Xba*I–*Sal*I fragment was excised. The corresponding sites were introduced into the M13-HuVHNP gene using oligonucleotides IV and VI, and the region between the sites was then exchanged. The sequence at the junctions was corrected with oligonucleotides VII and VIII, and an internal *Bam*HI site removed using the oligonucleotide IX, to create the M13-RaVHCAMP gene. The encoded sequence of the mature domain is thus identical to that of YTH 34.5HL. The reshaped heavy-chain variable domain (HuVHCAMP) was constructed in an M13 vector by priming with three long oligonucleotides simultaneously on the single strand containing the M13-HuVHNP gene[12,19]. Each oligonucleotide (X, XI and XIII) was designed to replace each of the hypervariable regions with the corresponding region from the heavy chain of the YTH 34.5HL antibody. Colony blots were probed initially with the oligonucleotide X and hybridization positives were sequenced; the overall yield of the triple mutant was 5%. The (Ser27 → Phe) and (Ser27 → Phe, Ser30 → Thr) mutants of M13mp8-HuVHCAMP were made with the mixed oligonucleotide XIII. The reshaped light-chain variable domain (HuVLCAMP) was constructed in M13 from a gene with framework regions based on human REI (J. Foote, unpublished data). As above, three long oligonucleotides (XIV, XV and XVI) were used to introduce the hypervariable regions of the YTH 34.5HL light chain.

Note: There are discrepancies involving the first framework region and the first hypervariable loop of the NEW heavy chain between the published sequence[12] used here and the sequence deposited in the Brookhaven data base (in parentheses): Ser27 (→Thr), Thr28 (→Ser) and Ser30 (→Asp). Neither version is definitive (R. J. Poljak, personal communication) and the discrepancies do not affect our interpretations.

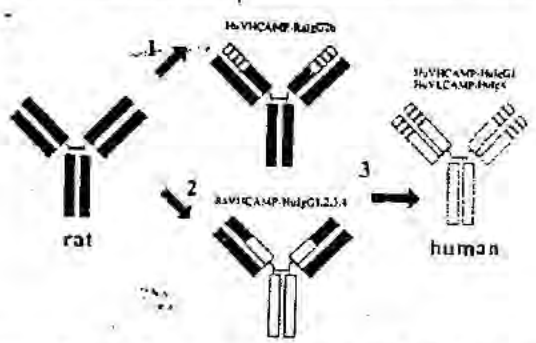

Fig. 2 Strategy for reshaping a human antibody for therapy. Sequences of rat origin are marked in black, and those of human origin in white. The recombinant heavy and light chains are also marked using a systematic nomenclature. See text for description of stages 1, 2 and 3. The genes encoding the variable domains were excised from the M13 vectors as *Hin*dIII–*Bam*HI fragments, and recloned into pSV2gpt[29] (heavy chains) or pSV2neo[30] (light chains), expression vectors containing the immunoglobulin enhancer[12]. The human γ1 (ref. 40), γ2 (ref. 41), γ3 (ref. 42), γ4 (ref. 41) and κ (ref. 36) and the rat γ2b (ref. 43) constant domains were introduced as *Bam*HI fragments. The following plasmids were constructed and transfected into lymphoid cell lines by electroporation[44]. In stage 1, the pSVgpt plasmids HuVHCAMP-RaIgG2B, HuVHCAMP(Ser→Phe)-RaIgG2B, HuVHCAMP-(Ser27→Phe, Ser30→Thr)-RaIgG2B were introduced into the heavy chain loss variant of YTH 34.5HL. In stage 2, the pSVgpt plasmids RaVHCAMP-RaIgG2B, RaVHCAMP-HuIgG1, RaVHCAMP-HuIgG2, RaVHCAMP-HuIgG3, RaVHCAMP-HuIgG4 were transfected as above. In stage 3, the pSV-gpt plasmid Hu(Ser27→Phe, Ser30→Thr)VHCAMP-HuIgG1 was co-transfected with the pSV-neo plasmid HuVLCAMP-HuIgK into the rat myeloma cell line Y0 (Y B2/3.0 Ag 20 (ref. 31). In each of the three stages, clones resistant to mycophenolic acid were selected and screened for antibody production by ELISA assays. Clones secreting antibody were subcloned by limiting dilution (for Y0) or the soft agar method (for the loss variant) and assayed again before 1 litre growth in roller bottles.

Since, to a first approximation, the sequences of hypervariable regions do not contain characteristic rodent or human motifs, such 'reshaped' antibodies should be indistinguishable in sequence from human antibodies.

There are mAbs to many cell-type-specific differentiation antigens, but only a few have therapeutic potential. Of particular interest is a group of rat mAbs directed against an antigen, the 'CAMPATH-1' antigen, which is strongly expressed on virtually all human lymphocytes and monocytes, but is absent from other blood cells including the haemopoietic stem cells[20]. The CAMPATH-1 series contains rat mAb of IgM, IgG2a and IgG2c isotypes[21], and more recently IgG1 and IgG2b isotypes which were isolated as class-switch variants from the IgG2a-secreting cell line YTH 34.5HL[22]. All of these antibodies, except the rat IgG2c isotype, are able to lyse human lymphocytes efficiently with human complement. Also the IgG2b antibody YTH 34.5HL-G2b, but not the other isotypes, is effective in antibody-dependent cell-mediated cytotoxicity (ADCC) with human effector cells[22]. These rat mAbs have important applications in problems of immunosuppression; for example control of graft-versus-host disease in bone-marrow transplantation[20]; the management of organ rejection[23]; the prevention of marrow rejection; and the treatment of various lymphoid malignancies (ref. 24 and M. J. Dyer, Hale, G., Hayhoe, F. G. J. and Waldmann, H., unpublished observations). The IgG2b antibody YTH 34.5HL-G2b seems to be the most effective at depleting lymphocytes *in vivo* but the use of all of these antibodies is limited by the anti-globulin response which can occur within two weeks of the initiation of treatment[24]. Here we describe the reshaping of human heavy and light chains towards binding the CAMPATH-1 antigen and the selection of human effector functions to match the lytic potential of the rat IgG2b isotype.

Table 1 Reshaping the heavy-chain variable domain

Heavy chain variable domain	Concentration of antibody in μg ml^{-1} at 50% antigen binding	50% complement lysis
RaVHCAMP	0.7	2.1
HuVHCAMP	27.3	*
HuVHCAMP (Ser27→Phe)	1.8	16.3
HuVHCAMP (Ser 27→Phe, Ser 30→Thr)	2.0	17.6

Antibodies with the heavy-chain variable domains listed above, rat IgG2b constant domains and rat light chains were collected from supernatants of cells at stationary phase and concentrated by precipitation with ammonium sulphate, followed by ion exchange chromatography on a Pharmacia MonoQ column. The yields of antibody were measured by an enzyme-linked immunosorbent assay (ELISA) directed against the rat IgG2b isotype, and each was adjusted to the same concentration[35]. To measuring binding to antigen, partially purified CAMPATH-1 antigen was coated onto microtitre wells and bound antibody was detected via a biotin-labelled anti-rat IgG2b mAb[35], developed with a streptavidin-peroxidase conjugate (Amersham). Complement lysis of human lymphocytes was with human serum as the complement source[21]. For both binding and complement assays, antibody titres were determined by fitting the data to a sigmoid curve by at least squares iterative procedure[21].

* Complement lysis with the HuVHCAMP variable domain was too weak for the estimation of lytic titre.

Strategy

The amino-acid sequences of the heavy- and light-chain variable domains of the rat IgG2a CAMPATH-1 antibody YTH 34.5HL were determined from the cloned complementary DNA (Fig. 1), and the hypervariable regions were identified according to Kabat[25]. In the heavy-chain variable domain there is an unusual feature in the framework region. In most known heavy-chain sequences Pro41 and Leu45 are highly conserved: Pro41 helps turn a loop distant from the antigen binding site and Leu45 is in the β bulge which forms part of the conserved packing between heavy- and light-chain variable domains[26]. In YTH 34.5HL these residues are replaced by Ala41 and Pro45 and presumably this could have some effect on the packing of the heavy- and light-chain variable domains. Working at the level of the gene and using three large mutagenic oligonucleotides for each variable domain, the rat hypervariable regions were mounted in a single step on the human heavy- or light-chain framework regions taken from the crystallographically solved proteins NEW[27] and REI[28] respectively (Fig. 1). The REI light chain was used because there is a deletion at the beginning of the third framework region in NEW. The reshaped human heavy- and light-chain variable domains were then assembled with constant domains in three stages (Fig. 2). This permits a step-wise check on the reshaping of the heavy-chain variable domain (stage 1), the selection of the human isotype (stage 2), and the reshaping of the light-chain variable domain and the assembly of human antibody (stage 3). The plasmid constructions were genomic, with the sequences encoding variable domains cloned as *Hin*dIII–*Bam*HI fragments and those encoding the constant domains as *Bam*HI–*Bam*HI fragments in either pSVgpt (heavy chain)[29] or pSVneo (light chain)[30] vectors. The heavy-chain enhancer sequence was included on the 5′ side of the variable domain, and expression of both light and heavy chains was driven from the heavy-chain promoter and the heavy-chain signal sequence.

Heavy-chain variable domain

In stage 1, the reshaped heavy-chain variable domain (HuVHCAMP) was attached to constant domains of the rat

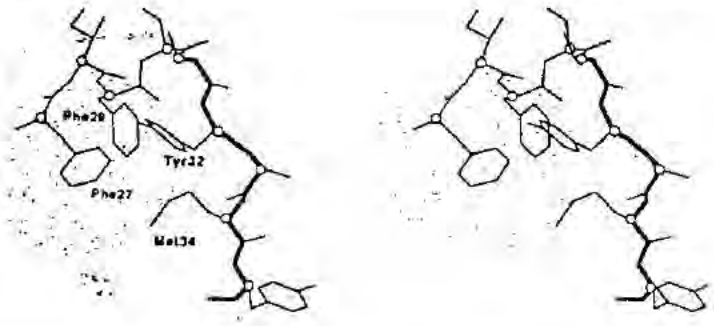

Fig. 3 Loop Phe27 to Tyr35 in the heavy-chain variable domain of the human myeloma protein KOL, which has been solved crystallographically[45]. The backbone of the hypervariable region according to Kabat[25] is highlighted, and a 200% van der Waal surface is thrown around Phe 27 to show the interactions with Tyr 32 and Met 34 of the Kabat hypervariable region. In the rat YTH 34.5HL heavy chain, these three side chains are conserved in character, but in HuVHCAMP, Phe27 is replaced by Ser.

isotype IgG2b and transfected into a heavy-chain loss variant of the YTH 34.5 hybridoma. This variant carries two light chains, one derived from the Y3 fusion partner[31]. The cloned rat heavy-chain variable domain (RaVHCAMP) was also expressed as above, and the antibodies were purified and quantified (Table 1). The HuVHCAMP and RaVHCAMP antibodies, each of the rat IgG2b isotype, were compared to the CAMPATH-1 antigen in a direct binding assay and in complement lysis of human lymphocytes (Table 1). Compared with the original rat antibody, or the engineered equivalent, the antibody with the reshaped heavy-chain domain bound poorly to the CAMPATH-1 antigen and was weakly lytic. This suggested an error in the design of the reshaped domain.

There are several assumptions underlying the transfer of hypervariable loops from one antibody to another[47], in particular the assumption that the antigen binds mainly to the hypervariable regions. These are defined as regions of sequence[25] or structural[32] hypervariability, the locations of hypervariable regions being similar by both criteria except for the first hypervariable loop of the heavy chain. By sequence the first hypervariable loop extends from residues 31–35 (ref. 25) whereas by structure it extends from residues 26–32 (ref. 32). Residues 29 and 30 form part of the surface loop, and residue 27, which is phenylalanine or tyrosine in most sequences, including YTH 35.5HL, helps pack against residues 32 and 34 (Fig. 3). Unlike most human heavy chains, in NEW (see note in Fig. 1) the phenylalanine is replaced by serine, which would be unable to pack in the same way. To restore the packing of the loop, we made both a Ser 27 → Phe mutation, and a Ser 27 → Phe, Ser 30 → Thr double mutation in HuVHCAMP. These two mutants showed a significant increase in binding to CAMPATH-1 antigen and lysed human lymphocytes with human complement (Table 1). Thus the affinity of the reshaped antibody could be restored by a single Ser 27 → Phe mutation, possibly as a consequence of an altered packing between the hypervariable regions and the framework. This suggests that alterations in the 'Kabat' framework region can enhance the affinity of the antibody and extends previous work in which an engineered change in the hypervariable region yielded an antibody with increased affinity[33].

Heavy-chain constant domains

In stage 2 (Fig. 2), the rat heavy-chain variable domain was attached to constant domains of the human isotypes IgG1, 2, 3 and 4, and transfected into the heavy-chain loss variant of the YTH 34.5 hybridoma. In complement lysis (Fig. 4*a*), the human IgG1 isotype proved similar to the YTH 34.5HL-G2b, with the human IgG3 isotype being less effective. The human IgG2 isotype was only weakly lytic and the IgG4 isotype was non-lytic. In ADCC (Fig. 4*b*) the human IgG1 was more lytic than the YTH 34.5HL-G2b antibody. The decrease in lysis at higher concentrations of the rat IgG2b and the human IgG1 antibody is due to an excess of antibody, which causes the lysis of effector cells. The human IgG3 antibody was weakly lytic, and the IgG2 and IgG4 isotypes were non-lytic.

We therefore selected the human IgG1 isotype for the reshaped antibody. Other recent work also favours the use of IgG1 isotype for therapeutic application. When the effector functions of human isotypes were compared using a set of chimaeric antibodies with an anti-hapten variable domain, the IgG1 isotype appeared superior to the IgG3 in both complement and cell-mediated lysis[15]. Also, of two mouse chimaeric antibodies with human IgG1 or IgG3 isotypes directed against cell surface antigens as tumour cell markers, only the IgG1 isotype mediated complement lysis[13,14].

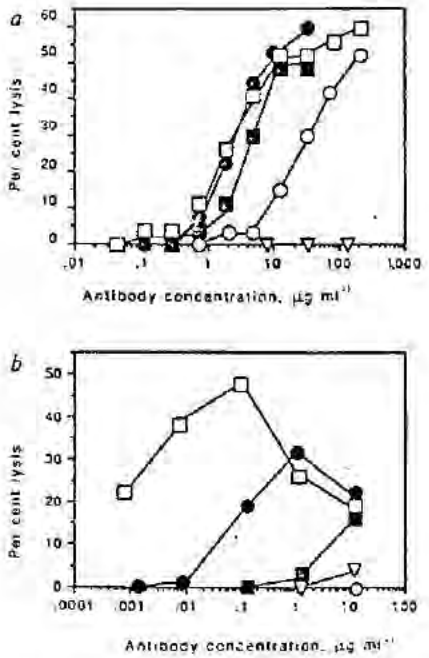

Fig. 4 *a*, Complement lysis and *b*, ADCC for antibodies with rat light-chain and rat heavy-chain variable domain attached to human IgG1 (□), IgG2 (○), IgG3 (■), or IgG4 (▽) isotypes. Lysis with the YTH 34.5HL antibody (●) is also shown.
Methods. Antibody was collected from cells in stationary phase, concentrated by precipitation with ammonium sulphate and desalted into phosphate buffered saline (PBS). Antibodies bound to the CAMPATH-1 antigen-coated on microtitre plates, were assayed in ELISA directed against the rat κ light chain[25], and each adjusted to the same concentration. The antibodies were assayed in complement lysis (Table 1) and ADCC with activated human peripheral blood mononuclear cells[35,46]. Briefly, 5×10^6 human peripheral blood cells were labelled with ^{51}Cr and incubated for 30 min at room temperature with different concentrations of antibody. Excess antibody was removed and a 20-fold excess of activated cells added as effectors. After 4 h at 37 °C cell death was estimated by ^{51}Cr release.

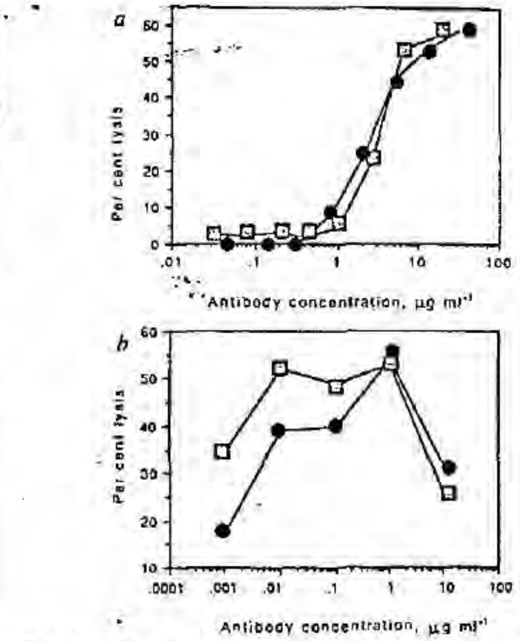

Fig. 5 *a*, Complement lysis and *b*, ADCC of the reshaped human (□) and rat YTH 34.5HL (●) antibodies. Antibody HuVHCAMP (Ser27→Phe, Thr30→Ser)-HuIGG1, HuVLCAMP-HuIGK was purified from supernatants of cells in stationary phase by affinity chromotography on protein-A Sepharose. The yield (about 10 mg l^{-1}) was measured spectrophotometrically. Complement and ADCC assays were performed as in Fig. 4.

Light chain

In stage 3 (Fig. 2), the reshaped heavy chain was completed by attaching the reshaped HuVHCAMP (Ser27→Phe, Ser30→Thr) domain to the human IgG1 isotype. The reshaped light-chain domain HuVLCAMP was attached to the human Cκ domain. The two clones were co-transfected into the non-secreting rat Y0 myeloma line. The resultant antibody, bound to CAMPATH-1 antigen (data not shown), and proved almost identical to the YTH 34.5HL-G2b antibody in complement lysis (Fig. 5*a*). In cell-mediated lysis the reshaped human antibody was more effective than the rat antibody (Fig. 5*b*). Similar results were obtained with three different donors of target and effector cells (data not shown). Also, the antibody was as effective as YTH 34.5HL-G2b in killing leukaemic cells from three patients with B-cell lymphocytic leukaemia by complement-mediated lysis with human serum. Thus, by transplanting the hypervariable regions from a rodent to a human antibody of the IgG1 subtype, we have reshaped the antibody for therapeutic application.

Prospects

The availability of a reshaped human antibody with specificity for the CAMPATH-1 antigen should permit a full analysis of the *in vivo* potency and immunogenicity of an anti-lymphocyte antibody with wide therapeutic potential. Even if anti-idiotypic responses are eventually observed, considerable therapeutic benefit could be derived from an extended course of treatment. Also, it should be possible to circumvent an anti-globulin response restricted to idiotype by using a series of antibodies with different idiotypes[34]. In principle, the idiotype of the reshaped CAMPATH-1 could be changed by altering the hypervariable regions or the framework regions—evidence from a reshaped antibody specific for the hapten nitrophenyl acetate suggests that recognition by anti-idiotypic antisera and anti-idiotypic mAbs is influenced by residues in the framework region[19]. Thus, recycling the hypervariable regions on different human framework regions should change the idiotype, although ultimately it might focus the response directly onto the binding site for the CAMPATH-1 antigen. Although such focusing would be undesirable for CAMPATH-1 antibodies, it could be an advantage for the development of anti-idiotypic vaccines. It is likely that the answers to some of these questions will emerge from the use of this reshaped antibody in therapy.

We thank J. Foote for the synthetic gene encoding the framework regions of a human light chain; P. Leder, T. R. Rabbitts, T. Honjo, M. P. Lefranc respectively for clones encoding the constant regions of human κ chain, human IgG2 and IgG4, human IgG1, human IgG3; G. Hale for CAMPATH-1 antigen and for advice; M. Bruggemann and M. S. Neuberger for subclones of the heavy-chain constant regions[15] and for advice; M. Frewin for technical assistance and C. Milstein for encouragement. L.R. is supported by a fellowship from the German 'Sonderprogramm Gentechnologie des DAAD'. The work was supported by the Medical Research Council and by Wellcome Biotechnology Ltd. 'CAMPATH' is a trademark of The Wellcome Foundation Ltd.

Received 3 December 1987; accepted 12 February 1988.

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5-18-94 DrShore

27/E B.White 5-20-94 (WE)

DOCKET NO.: CARP-0009 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

John R. Adair, et al.

Serial No.: 07/743,329 Group Art Unit: 1807

Filed: September 17, 1991 Examiner: L. Bennett Arthur

For: HUMANISED ANTIBODIES

I, Doreen Yatko Trujillo, Registration No. 35,719 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

On May 9, 1994

Doreen Yatko Trujillo

Doreen Yatko Trujillo, Reg. No. 35,719

K Foster 5-23-94 B.W. 9/28/94 B.White

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

RECEIVED
MAY 13 1994

Dear Sir:

RESPONSE TO ADVISORY ACTION

In the claims:

Please amend claim 67 as follows:

In claim 67, line 4, after "chain", please insert --framework--.

REMARKS

This paper is being filed in response to the Advisory Action mailed February 25, 1994, pursuant to Examiner Arthur's suggestion during a teleconference. This response is being filed in order to reduce the number of issues to be addressed upon

appeal. It is believed that no petition or extension fee is required, since the response is being filed within two months of the "Notice of Appeal". To the extent this belief is erroneous, please charge any fees due to Deposit Account No. 23-3050.

In the Advisory Action, Examiner Arthur stated that the deletion of the recitation "acceptor antibody heavy chain [framework] resides [sic]" changes the scope of the claimed invention to more broadly encompass composite antibodies in which the acceptor contributes more than just the framework. During a teleconference, the Examiner clarified that she was referring to the deletion of the word "framework", and not suggesting that the entire recitation in quotes had been deleted. Accordingly, Applicants have amended claim 67 to reinsert the word "framework" where it had been previously deleted.

The Examiner also stated, in the Advisory Action, that the deletion changed the scope such that the "...donor antibody is no longer limited to donating the antigen binding residues. The specification does not appear to support this broader concept." The Examiner, therefore, asserted that the amendment raised new matter and a new scope rejection under 35 U.S.C. § 112, first paragraph.

During the teleconference, the undersigned explained that the donor antibody was *never* limited to contributing the antigen

binding residues. The Examiner suggested submission of the present response to clarify this point and make the foregoing amendment.

On page 17, line 15, of the application as filed, the following is stated: "The positions at which donor residues are to be substituted for *acceptor* residues are then chosen as follows." (Emphasis added.) The text following this passage discloses which residues in the **framework** are to be changed, in addition to those changes to be made in the CDRs.

In paragraph 2.1 on the same page, residues 23, 24, 49, 71, 73, and 78 in the heavy chain variable domain are listed to be changed. In a previous paragraph, numbered 1, the residues of the CDRs (i.e. antigen binding residues) are listed for the heavy chain. As can be seen, the residues to be changed do not occur in the CDRs and are, therefore, in the framework region. Claim 1 as originally filed recited changing these residues to donor. Contrary to the Examiner's interpretation, the claimed invention was never limited to changes to donor only within the antigen binding residues.

Neither the Advisory Action, nor the teleconference, specifically addressed the remaining rejections. It appears, however, that the rejections stand "for the reasons of record." (See item #4, Advisory Action.) Applicants do not wish to reiterate the whole Amendment here, but would like to emphasize

some points in the interest of possibly reducing issues to be addressed on appeal.

The first point concerns the specification of acceptor residues in the claims. It was previously believed, as a result of an interview, that the Examiner thought the claims as drafted covered the situation in which all the variable domain residues are donor -- i.e., chimeric antibodies. Thus, the Applicants specified residues which are to remain as acceptors. As discussed in the Amendment, this is implicit, if not explicit, from the application as filed.

Further, the claims specify that the variable domain comprises donor and acceptor sequences. This specification distinguishes the antibodies of the claims from chimerics. In chimerics, the variable domain is comprised entirely of donor residues.

Now, however, it appears the Examiner thinks the claims had previously been limited to antibodies in which the residues in the CDRs are donor, and the remaining residues are acceptor. This is inconsistent with the specification and claims as well as the prior Office Actions and suggests further discussion is merited.

Applicants would also like to clarify a point regarding the Queen reference. Panels A and B on page 10003 of Queen refer to the light and heavy chains, respectively, of the acceptor antibody (upper sequences) and the humanized anti-TAC antibody

(lower sequences). The attached panels correspond to Panels A and B of Queen. The upper and lower sequences are further separated in the attached, the lower sequence representing the humanized antibody. The numbers above the sequences utilize the linear numbering system. The numbers below utilize Kabat numbering. Queen donor residues are indicated in red. Applicants' donor residues are indicated in blue. As can be seen, the two approaches are very different particularly for the heavy chain.

During the teleconference, the Examiner also indicated that she would be amenable to conducting an interview with the Applicants upon return from her upcoming leave. It was further indicated that her return would be sometime in May. Applicants still wish to conduct an interview and respectfully request a prompt communication thereafter regarding scheduling so that appropriate arrangements can be made.

Respectfully submitted,

Doreen Yatko Trujillo

Doreen Yatko Trujillo
Registration No. **35,719**

Date: **May 9, 1994**

+8352

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A

QUEEN ET AL - SEQUENCES FROM FIGURE 2 - NUMBERING IN PAPER ABOVE
NUMBERING ACCORDING TO KABAT BELOW

PANEL A - UPPER SEQUENCE

```
1                   10                  20                  30
D I Q M T Q S P S T L S A S V G D R V T I T C R A S Q S I N T W L A
1                   10                  20  23              30

        40                  50                  60
W Y Q Q K P G K A P K L L M Y K A S S L E S G V P S R F I G S G S G
        40                  50                  60

 70                  80                  90                  100
T E F T L T I S S L Q P D D F A T Y Y C Q Q Y N S D S K M F G Q G I
 70                  80                  88  90                  100

      107
K V E V K
      107
```

PANEL A - LOWER SEQUENCE

```
1                   10                  20                  30
Q I V L T Q S P A I M S A S P G E K V T I T C S A S S S I S Y M H W
1                                                   23          35

        40                  50                  60
F Q Q K P G T S P K L W I Y T T S N L A S G V P A R F S G S G S G T
        40                  50                  60

 70                  80                  90                  100
S Y S L T I S R M E A E D A A T Y Y C H Q R S T Y P L T F G S G T K
70                  80                  88  90                  100

    106
L E L K
    107
```

B

PANEL B - UPPER SEQUENCE

```
1                 10                  20                  30
Q V Q L V Q S G A E V K K P G S S V K V S C K A S G G T F S R S A I
1                 10                  20  22              30

        40                  50                  60
I W V R Q A P G Q G L E W M G G I V P M F G P P N Y A Q K F Q G R V
 36

 70                  80                  90                  100
T I T A D E S T N T A Y M E L S S L R S E D T A F Y F C A G G Y G I
                          82 a b c            90  92

           110         117
Y S P E E Y N G G L V T V S S
100               110   113
```

PANEL B - LOWER SEQUENCE

```
1                 10                  20                  30
Q V Q L Q Q S G A E L A K P G A S V K M S C K A S G Y T F T S Y R M
                                      22

        40                  50                  60
H W V K Q R P G Q G L E W I G Y I N P S T G Y T E Y N Q K F K D K A
                            52 a                60

 70                  80                  90                  100
T L T A D K S S S T A Y M Q L S S L T F E D S A V Y Y C A R G G G V
                          82 a b c            92  94

          110         116
F D Y W G Q G T T L T V S S
103               113
```

(There is a deletion in the Kabat system between F and D at beginning of last line.)

DOCKET NO.: CARP-0032 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

35/D
D.J
11/17/94

In re application of:

John Robert Adair, Diljeet Singh Athwal and John Spencer Emtage

Serial No.: N/A Group Art Unit: 1807

Filed: Herewith Examiner: B. Sisson

For: HUMANISED ANTIBODIES

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT

Pursuant to 37 C.F.R. § 1.115, prior to examination of the above-identified patent application, please amend the claims as follows.

In the claims:

Please cancel claims 67 - 72, 108, and 114 without prejudice.

Please add claims 120 - 127, as follows:

-- 120. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in

a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues, ~~provided that the antibody does not have affinity for the p55 chain of the human interleukin 2 receptor~~.

~~121~~. The antibody molecule of claim ~~120~~, wherein amino acid residues 26 to 30 and 59 to 65 in said composite heavy chain are additionally donor residues.

~~122~~. The antibody molecule of claim ~~120~~, wherein amino acid residues 71, 73, and 78 in said composite heavy chain are additionally donor residues.

~~123~~. The antibody molecule of claim ~~120~~, wherein at least one of amino acid residues 1, 3, and 76 in said composite heavy chain are additionally donor residues.

~~124~~. The antibody molecule of claim ~~120~~, wherein at least one of amino acid residues 36, 94, 104, 106, and 107 in said composite heavy chain are additionally donor residues.

~~125~~. The antibody molecule of claim ~~124~~, wherein at least one of amino acid residues 2, ~~4~~, 6, 38, 46, 67, and 69 in said composite heavy chain are additionally donor residues.

~~126~~. The antibody molecule of claim ~~120~~, wherein said complementary light chain is a composite light chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody light chain framework residues, the remaining light chain residues corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite light chain; said CDRs comprise donor residues at least at residues 24 to 34, 50 to 56, and 89 to 97; and amino acid residues 46, 48, 58, and 71 at least are donor residues.

~~127~~. The antibody molecule of claim ~~126~~, wherein amino acid residues 1, 3, 60 (if this residue can form a salt bridge with residue 54), and 70 (if this residue can form a salt bridge with residue 24) in said composite light chain are additionally donor residues.--

REMARKS

The present application is a continuation of U.S. Application Serial No. 07/743,329 (hereinafter the "'329 application") under 37 C.F.R. § 1.62.

Claims 67 - 72, 108, and 114 were pending in the '329 application. Those claims have been cancelled in the present amendment. Applicants reserve the right to pursue the subject matter of the cancelled claims in continuation or divisional applications, as may be appropriate.

Claims 120 - 127 are being submitted in the present amendment. Support for the amendments is found in the application as originally filed as indicated below. In claims 120 and 126, the specification that the variable domain "predominantly" comprises "human acceptor framework residues" is supported by, *inter alia*, page 3, lines 16 - 21, of the application as originally filed. The problems attendant to chimerics are therein described. It is also clear from the number of framework residues discussed as being changed to donor that the framework residues remain, predominantly, acceptor. Support for the residues specified as donor in claim 120 can be found, *inter alia*, on page 7, first full paragraph, page 19, Section 1, and page 46, Section 15.2.1. Support for the residues specified as donor in claim 126 can be found, *inter alia*, on page 17, lines 12 to 14 and page 18, Section 3.1.

As to the remaining claims, support for the residues specified as donor in claim 121 can be found, *inter alia*, on page 8, middle paragraph and page 17, Section 1. Support for the residues specified as donor in claim 122 can be found, *inter alia*, on page 7, first full paragraph. Support for the residues specified as donor in claim 123 can be found, *inter alia*, on page 20, Section 2.1.1. Support for the residues specified as donor in claim 124 can be found, *inter alia*, on page 21, lines 10 to 12. Support for the residues specified as donor in claim 125 can be found, *inter alia*, on page 21, lines 13 to 16. Support for the residues specified as donor in claim 127 can be found, *inter alia*, on page 21, lines 3 to 7.

In a helpful telephonic discussion on June 2, 1994 between Examiner Sisson and the undersigned, Examiner Sisson expressed his reservations regarding specification of acceptor residues in the claims. The present claims do not specify acceptor residues. It is expected that this concern has been obviated.

Alternatively, the present claims specify that the variable domain comprises "**predominantly** human acceptor antibody heavy chain framework residues". It is, thus, asserted that any concerns regarding the claims encompassing chimeric antibodies in which the entire variable domain is of donor origin have been obviated.

The Examiner also indicated during that discussion that his concerns were more directed to issues of scope and that, if the claims contained critical limitations not taught in the art, the art rejections would not be a problem.

Applicants believe that, in light of the amendments, the application is now in condition for allowance and request early notification of the same. To the extent this belief is erroneous, Applicants request that the Examiner contact the undersigned at (215) 564-8352 to discuss the same.

Respectfully submitted,

Doreen Yatko Trujillo

Doreen Yatko Trujillo
Registration No. 35,719

Date: **September 7, 1994**

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DOCKET NO.: CARB-0032 PATENT

39/H
B. Denny
10/20/95

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

John Robert Adair, Diljeet Singh Athwal, and John Spencer Emtage

Serial No.: 08/303,569 Group Art Unit: 1806

Filed: 9/07/94 Examiner: D. Adams

For: HUMANISED ANTIBODIES

I, Doreen Yatko Trujillo, Registration No. 35,719 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

On September 18, 1995

Doreen Yatko Trujillo

Doreen Yatko Trujillo, Esquire Reg. No. 35,719

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

AMENDMENT

Please amend the application as follows.

In the Specification:

Page 1, line 2, after "filed September 17, 1991", please insert -- , now abandoned --.

Please insert new page 94.

In the Claims:

Claim 120, line 12, please delete, ", provided that the antibody does not have affinity for the P55 chain of the human interleukin 2 receptor."

REMARKS

This paper is being filed in response to the Office Action mailed on May 16, 1995. The following comments use the section numbering set forth in the Office Action. Applicants respectfully request reconsideration and withdrawal of all rejections.

CLAIM AMENDMENT

As will be shown below, a reference which the Examiner initially asserted as prior art was not published before the priority date. The "provided that .... " clause in claim 120 was inserted in view of this reference. Since the rejection over this reference is not proper, claim 120 has been amended accordingly.

Sections 15 to 18

The contents of these sections are noted. No action is required.

Section 19

It is believed that this point has been taken care of by the amendment to the description.

Section 20

The Abstract has been added in the required form on new page 94. The text of the abstract is found on the cover page of the PCT publication from which the present application derived and, therefore, does not represent new matter.

Sections 21 to 23

In these sections, the Examiner raises objections to the description and claims under 35 USC § 112, first paragraph. The Examiner alleges that the specification fails to provide an enabling disclosure. However, it appears that the Examiner is actually questioning whether the invention will work over the entire of the scope of the claims.

As regards enablement, the first paragraph of § 112 requires that a person skilled in the art should be able to make and use the invention. In order to make and use the invention, the skilled person needs to be able to carry out the following steps, all of which are clearly set out in the specification.

1. Obtain a donor antibody having affinity for a predetermined antibody. This can best be done either by obtaining a hybridoma, for instance from a culture collection such as the ATCC, or by producing a hybridoma, using the well established Kohler-Milstein procedure.

2. Determine the sequences of the variable domains of the heavy and light chains of the donor antibody. As shown in the specification, this can best be achieved by isolating cDNA from the hybridoma, sequencing the cDNA and decoding the cDNA to give

the amino acid sequence.

3. Number the amino acid sequences from the donor antibody according to the Kabat numbering system. For any person of skill in the art, this is a simple matter, as the Kabat numbering system was well established at the priority date of the application. Thus, the skilled person would readily be able to identify the donor residues specified in the present claims.

4. Determine the amino acid sequences of the variable domains of a human antibody. This is again a simple matter as the sequences of a large number of human antibodies have been published, for instance by Kabat. Thus, this merely requires the skilled person to look in a readily available reference book. Alternatively, the skilled person would look in any one of a large number of papers disclosing the sequences of human antibodies.

5. Number the human amino acid sequences. Quite often, this had already been done. In any event, the comments in 3 above apply.

6. Determine the composite sequence(s) in accordance with the instructions in the claims. This merely requires comparison of the numbered sequences of steps 3 and 5.

7. Produce DNA molecule(s) encoding the composite sequence(s) determined in step 6. This is a matter of standard recombinant DNA technology. The DNA molecule(s) could be produced by total synthesis, partial synthesis or mutagenesis techniques, all of which were well know in the art at the priority date.

8. Transform a suitable host cell with the DNA sequence(s) produced in step 7 such that the host cell expresses the DNA sequence(s). This again is a matter of standard recombinant DNA technology.

It is to be noted that the present specification discloses copious details how to carry out all these steps. For instance, on page 25, there is a description of how to grow

hybridomas. On page 30, there is a description of cDNA preparation and screening, with details of probes to be used. Page 31 discloses details of DNA sequencing and production of expression vectors. Page 36 gives details of expression. Further on in the specification, even more detailed instructions are provided for the production of antibodies as defined in the present claims.

The procedures disclosed in the present specification could have been applied by any skilled person at the priority date for any available donor antibody or for any donor antibody the skilled person could have produced. The skilled person is told exactly what to do and how it can be done. The skilled person is given a number of examples to follow. It cannot be seen that this would require "undue experimentation".

The Examiner has not pointed to any step in the disclosed processes which could not have been carried out by a person of skill in the art. If the Examiner believes that any particular one or more of the steps could not have been carried out by a person of skill in the art, it is requested that the Examiner provide evidence of the same or, if in the Examiner's knowledge, provide an affidavit, both pursuant to 37 C.F.R. §1.107.

It is submitted that, in the absence of any evidence to the contrary, it must be accepted that the skilled person could have started with any donor antibody and followed the instructions in the specification to produce an antibody as now claimed.

The Examiner's real point appears to be that he does not believe that carrying out the steps referred to above would always lead to the production of a useful antibody. However, the Examiner has provided no evidence to support his belief; nor is this a requirement for enablement. *In re Sarrett*, 140 U.S.P.Q. 474 (C.C.P.A., 1964), *reh'g denied*. ". . . the mere *possibility* of inclusion of inoperative substances does not prevent *allowance* of broad claims." (emphasis in original) *Id.*, 140 U.S.P.Q. at 486.

Regardless, as the Examiner has pointed out in Section 22 (A) of the Office Action, the present specification provides a number of examples in which the procedure described in the specification has been applied successfully. The specification has examples relating to OKT3, OKT4A, B72.3 (an anti-mucin MAb), R6-5-D6 (an anti-ICAM-1 MAb) and 61E71 hTNF1, hTNF3 and 101.4 (all anti-TNF MAbs). Thus, the specification by itself provides examples in which MAbs against a variety of different antigens have been successfully humanised.

The Examiner is also referred to the enclosed Declaration executed by Dr. G. T. Yarranton (who the Examiner met during interviews on other cases last year). This declaration provides further evidence that the Applicants' employers have successfully used the procedure disclosed in the specification to humanise 17 antibodies.

The Examiner cannot point to a single example where anyone has tried to use the procedure set forth in the present specification and has failed to produce a useful antibody. The Examiner has merely referred to three papers which do not even try to put the Applicants' invention into effect. It is submitted that this does not provide any evidence that the procedure set forth in the present specification cannot be applied to any antibody. It is the *claimed invention* which is relevant to an analysis of enablement. *Ex parte Ehrlich*, 3 U.S.P.Q. 2d 1011 (Bd. Pat. App's. Int. 1987).

The first paper to which the Examiner refers is Reichmann et al. (Nature, 372, 323-327, 1988). This paper shows the results of "reshaping" the rat monoclonal antibody YTH34.5HL. As can be seen from Table 1 in the right hand column on page 325, Reichmann made four heavy chain constructs. The first (RaVHCAMP) is a chimeric heavy chain having the rat heavy chain domain fused to a human constant region. In the other three constructs, the heavy chain variable domain is predominantly of human origin but all three CDRs (residues 31 to 35, 50 to 58 and 95 to 102) correspond to those of the rat antibody. In the second construct, only the CDRs are rat residues. In the third construct, in addition to changing the CDRs, residue 27 has been changed to a more usual human residues (Ser → Phe). In the fourth construct, in addition to changing the CDRS, residues 27 and 30 have been changed to more

usual human residues (27 Ser → Phe, 30 Ser → Thr). In the light chain construct only the CDRs are changed to rat.

It can thus be seen that Reichmann does not disclose a procedure which leads to an antibody as defined in the present claims. As far as the heavy chain is concerned, Reichmann does not even mention Kabat residues 23, 24 and 49, let alone change them to the rat residues. Reichmann did not carry out a procedure as set forth in the present specification and thus Reichmann does not provide any evidence which shows or suggests that the present procedure cannot be put into practice for any antibody.

The second paper to which the Examiner refers is Queen et al. (PNAS-USA, 86 10029-10033, 1989). However, as is discussed in more detail below, Queen et al. is not prior art. Nonetheless, to the extent Queen et al. is contemporaneous, it will be discussed. Queen adopts an entirely different approach than that set forth in the present specification. This can be seen from the passage in the right hand column on page 10031 headed "Construction of a Humanised Anti-Tac Antibody". The first step in this approach is to select human acceptor sequences which are *as homologous as possible* to the mouse donor antibody. The second step is to use the donor CDRs in the human acceptor sequence. The third step is to carry out molecular modelling and then to select donor residues, to be put into the acceptor sequences, on the basis of various criteria. This leads to a composite variable domain sequence which

contains a large number of donor residues. Although the procedure used by Queen is different from that disclosed in the present specification, in the heavy chain, the CDRs and residues 23, 24 and 49 all correspond to those residues in the donor mouse antibody. Thus, the humanised antibody of Queen is, to a certain extent, in accordance with the present invention.

However, the foregoing residues were not the only residues transformed to donor in Queen. This point was acknowledged by the Examiner on page 4, lines 35-36, of the Office Action. It is to be noted that Queen's humanised antibody has only one third of the affinity of the donor mouse antibody. This is not a particularly good result as the aim of any humanisation procedure is to recover the same affinity as that of the donor antibody. It is believed that the reason for such a low recovery of affinity by Queen is due to there being too many donor residues in the acceptor frameworks. It is believed that, had the procedure of the present specification been adopted, certain of these residues would not have been changed, and improved recovery of affinity would have been obtained.

Nevertheless, given the above explanation of the low recovery affinity in Queen, it can be seen that, if anything, Queen shows that following the procedure of the present specification will lead to the production of useful antibodies

In passing, it is to be noted that the Examiner appears to be laboring under a misconception. The Examiner refers in Section 22 (A) to the changes resulting "in increased antigen binding affinity". The present Applicants do not claim that using the procedure of the specification will result in increased affinity. The aim of the invention is to provide an antibody having equivalent affinity to that of the donor antibody, but with increased human compatibility. The problem with mouse or rat antibodies is not that they have low affinity. They generally have very good affinity. The problem is that they are not compatible with humans. Thus, the problem is to retain the affinity but to remove human incompatibility.

It is no doubt true that, in some cases, it is possible to increase the affinity of the antibody by using the procedure of the present specification. However, this is a bonus effect and is not the object of the invention. Thus, while recovering one third of affinity may not be acceptable, recovering close to 100% of activity is more than enough. It is therefore suggested that the Examiner should look at the present invention in terms of recovering, not increasing, affinity. Nonetheless, an increase in affinity is an unexpected result relevant to nonobviousness.

Returning to the main theme of this Section the Examiner finally relies on Chothia et al. (J. Mol. Biol., 196, 901917, 1987). However, this has no bearing at all on whether the present

invention is applicable to any donor antibody.

Chothia describes theoretical work carried out on the structures and sequences of known antibodies or antibodylike molecules. These are all "natural" molecules in that they have not been in any way engineered. Chothia studied the resolved crystallographic structures of some of these molecules and also compared the sequences of the molecules. Most of the work was concerned with the conformation of the antigen-binding loops (L1 to L3 and H1 to H3). Chothia arranged the loops into groups, called "canonical structures".

Chothia also looked at the framework regions to a certain extent and identified certain framework residues which appeared to be involved in positioning the loops. However, Chothia appears to believe that these residues are specific to the loops with which they are associated. There is no indication that it is possible to make any predictions on the basis of these observations.

It can thus be seen that Chothia did not make any composite antibody chains, nor did Chothia produce any antibody chains by recombinant DNA technology. Most importantly, Chothia did not even attempt to produce a composite antibody chain using the procedure of the present specification. Thus, Chothia provides absolutely no evidence that one skilled in the art could not apply the teachings given in the present specification to any donor antibody.

It is submitted that the disclosures in Reichmann and Queen are relevant in one sense, in that they clearly show that, at the priority date, the skilled person was able to carry out all the necessary steps, for instance using recombinant DNA technology, to produce composite antibody chains. Thus, Reichmann and Queen support the Applicants' view that the present specification provides an enabling disclosure.

It is submitted that the Examiner's objection under Section 112 confuses the requirement for an enabling disclosure with the requirement for the invention to be nonobvious. As to enablement, the question to be asked is whether the skilled person, given the teaching in the specification, could have put that teaching into effect. In the present case, it is clear that the skilled person was able to carry out the necessary steps to produce an antibody according to the claims, using any donor antibody. Moreover, the present specification clearly shows that the procedure disclosed therein had been used successfully to produce a number of humanised antibodies having affinity equivalent to that of the donor antibody. Thus, on the basis of the teaching in the specification, the skilled person had every reason to expect that the procedure would be applicable to any donor antibody. As has been shown above, the prior art does not provide any evidence to suggest otherwise.

It is no doubt true, as the Examiner stated in Section 22 (A), that the prior art does not teach that a standardized principle is possible. However, this has no relevance to the question of enablement, because the prior art does not include the disclosure in the present specification. Absent the disclosure in the present specification, the skilled person would not have been taught that there was a standardized principle. This merely shows that the claimed subject matter is non-obvious. It does not show that the teaching in the present description is non-enabling.

In summary, it is submitted that:

(i) the present specification provides all the instructions necessary to enable the procedure disclosed therein to be put into effect for any donor antibody;

(ii) Reichmann and Queen confirm that, at the priority date, the skilled person was able to carry out the disclosed procedure;

(iii) the present specification shows that the disclosed procedure had been applied successfully to a number of donor antibodies, thus providing the skilled person with a reasonable expectation that the procedure is applicable to any donor antibody;

(iv) there is no evidence to show that the procedure is unsuccessful; and

(v) the prior art is not relevant to the skilled person's expectation of success because it does not include the disclosure in the present specification.

It is therefore submitted that the present specification provides an enabling disclosure for the whole scope of the claims.

For the above reasons, it is respectfully requested that the rejection under 35 USC § 112 against the specification and claims be withdrawn.

Section 25

The Applicants confirm the Examiner's presumption that the subject matter of all the claims was commonly owned at the time the inventions covered by the claims were made.

Sections 26 and 27

The Examiner's raising of a provisional obviousness-type double patenting rejection is acknowledged. This will be dealt with, probably by use of a terminal disclaimer, once the Examiner has acknowledged that the claimed subject matters in this and the co-pending application are patentable.

Section 28

In Section 28, the Examiner rejected all the claims as allegedly being obvious over Reichmann (see above), Queen (see above) and Waldmann (sic) (EP-A-0 239 400). It is presumed that the Examiner correctly cited the European patent application number (EP-A-0 239 400) for the third reference. If this is the case, the applicant is Winter. The Applicants therefore assume that the name for the third reference should be Winter. If this is not the case,

the Examiner is requested to identify the Waldmann paper to which he refers.

As a preliminary point, it is submitted that Queen et al. is not part of the prior art. The attached Declaration by the undersigned attorney shows that Queen was not published before the priority date of the present application. Thus, Queen cannot be used to attack the present claims.

The present application is a national phase filing of a PCT application claiming a foreign priority date of December 21, 1989. As indicated in the attached Declaration of the undersigned, the journal volume in which the Queen et al. reference appeared was not mailed until December 20, 1989. The journal was mailed by second class mail. Accordingly, no addressee could have received the journal *before* December 21, 1989.

As the Examiner is aware, magazines are effective as of the date they are received, not the date they are mailed. M.P.E.P. § 715.01(c). As no addressee could have received the reference before the foreign priority date, no addressee could have been in possession of the reference such that the subject matter sought to be patented as a whole would have been obvious "at the time the invention was made."[1] Indeed, in *Protein Foundation, Inc. v. Brenner*, 151 U.S.P.Q. 561 (D.D.C. 1966), the court took judicial

[1] In that regard, the time differential is also emphasized. The priority application was filed in the United Kingdom. The reference volume was mailed in the United States.

notice of the fact that second class mail does not travel and is not distributed as fast as first class mail. The court concluded that no magazine was delivered two days after being mailed in bulk. *Id.*, at 562. Regardless, it is emphasized that Queen et al. discloses that only 1/3 of the affinity of the murine antibody was recovered in their slightly less "human" antibody, and that "further work" was needed.

Since Queen is not part of the prior art, it is presumed that the Examiner's obviousness rejection can only be based on Reichmann and Winter. Before discussing those references in details, the Examiner is referred to Section 22 (A) of the Office Action, wherein the Examiner himself states that:

> The prior art does not teach that a standardized principle of which amino acids must always be changed is possible, but instead appears to teach that three dimensional structures of the antibodies and an understanding of protein folding properties is necessary to reasonable (sic) predict which amino acids will be effective in retaining antigen binding ability for a particular antibody.

It is submitted that this statement completely undermines the Examiner's position on obviousness. If the skilled person is not taught that a standardized principle is possible, it cannot be seen how the present invention, directed to a standardized principle, can be obvious.

It is also to be pointed out that the present invention, as set forth in the claims, is not that it will be necessary to

change some (unspecified) framework residues. The invention is that it will be necessary to change certain, carefully specified framework residues. Thus, the Examiner has to go beyond showing that a standardized principle was possible and has to show that the skilled person would inevitably have been led to the residue changes set forth in the present claims. As the Examiner admits in Section 28 of the Office Action:

> Neither Reichmann et al. or Queen et al. teach all of the exact mutations found in the claimed antibodies.

It thus cannot be seen how it can be obvious to get to the present invention.

This conclusion is reinforced if the prior art references cited by the Examiner not including Queen are properly considered. It is firstly to be pointed out that Winter was published in 1987, whereas Reichmann was published in 1988. Moreover, one of the authors of Reichmann is Dr. Winter, the sole inventor of Winter. It can thus be clearly seen that Reichmann follows on from the work of Winter. It is therefore believed that it is appropriate to discuss Winter first and then Reichmann as this reflects the way in which the art developed.

Winter teaches the basic concept of CDR-grafting. Thus, Winter clearly teaches the production of a grafted antibody in which only the CDRs (as defined by Kabat) from a donor antibody are grafted into an acceptor antibody in place of its natural CDRs.

There are examples in the citation showing this CDR grafting procedure. It is to be noted that in the examples, it is only the CDRs which are changed. No changes at all are made in the framework regions.

It is no doubt true that Winter contains a passage from page 7, line 25 to page 8, line 18 which refers to the possibility that framework residues may need to be changed. However, this passage is entirely devoid of any practical teaching. It does not mention a single residue number, nor does it even mention possible locations for such residues. Thus, Winter provides absolutely no suggestion, much less guidance, as to where to look for framework residues which may need changing.

The Examiner has asserted in Section 22 (A) of the Office Action that:

> ... it would require undue experimentation for a person of ordinary skill in the art to practice applicant's claimed invention from what has been disclosed in the specification.

Although the Applicants believe, for the reasons set forth above, that this is not true of the present specification, it is submitted that the Examiner's assertion applies with full force to Winter. The passage in Winter is merely an invitation to carry out further experiments without providing any directions or even hints as to how to carry out such experiments. It is therefore

submitted that the present claims are not at all obvious over Winter.

Turning now to Reichmann, it can be seen that this follows on from Winter. The first construct made by Reichmann is one in which only the donor CDRs are grafted into the acceptor frameworks. This construct is HUVHCAMP. As can be seen from Table 1, the first construct was nearly 40 times worse at binding antigen than the original rat antibody and was immeasurably worse in a complement binding assay. Reichmann therefore produced two more constructs. HuVHCAMP (Ser 27 → Phe, Ser 30 → Phe) and HuVHCAMP (Ser 27 → Phe, Ser 30 → Thr). The further changes in these constructs significantly improved both antigen binding and complement activation, but not to the level of the rat antibody.

The reason for making the further mutations at positions 27 and 30 is set forth in the left-hand column on page 326 of Reichmann. It can be seen that, at residue 27, the human acceptor sequence was unusual. Residue 27 was therefore changed to the more usual human residue. The change at residue 30 was made to bring the extended CDR, including the surface loop (residues 26 to 32) as well as the Kabat CDRs (residues 31 to 35) into conformity with those of the rat antibody. Thus, one mutation has the effect of making the grafted antibody look more human. The other mutation has the effect of extending CDR1.

It cannot be seen how this can in any way suggest the present invention. At best, it suggests that it would be better to define CDR1 as being residues 26 to 35 in the heavy chain. However, this certainly does not teach a general principle of changing framework residues and in particular it does not suggest that the particular framework residues of the present claims should be altered.

The passage on page 326 of Reichmann ends with the following sentence.

> This suggests that alterations in the 'Kabat' framework region can enhance the affinity of the antibody and extends previous work in which an engineered change in the hypervariable region yielded an antibody with increased affinity. (emphasis added).

Again, this is merely a suggestion for further work. It does not provide any hint or direction as to how the work should proceed. The only teaching is to extend CDR1 to include the surface loop. Thus, this certainly does not even remotely suggest the specific residue changes of the present claims.

The Examiner asserts that:

> ..... it would have been prima facie obvious ..... to apply the teachings of Winter to those of Reichmann .....

However, the Examiner appears to have failed to appreciate that the teaching of Winter is already contained in Reichmann. In fact, the teaching of Reichmann is based on the teaching of Winter. The

teaching of Winter was also published in Jones et al. (Nature, 321, 522-525, 1986), of which Winter is a co-author. Jones is reference 19 in Reichmann and is referred to in the paragraph bridging pages 323 and 325 of Reichmann. This paragraph makes it clear that Jones (and thus Winter) provided the basis for the work reported by Reichmann. Thus, the obvious combination of Winter and Reichmann had already been made in the prior art. However, despite having the expertise of Winter to call on, Reichmann comes nowhere near the present invention. It is therefore submitted that Reichmann by itself proves that a combination of Winter and Reichmann does not lead to the present invention.

Accordingly, Applicants submit that the Examiner has not established a *prima facie* case of nonobviousness of Applicants invention, with or without the Queen et al. reference. In fact, the Examiner's arguments under 35 U.S.C. §112 support this. Alternatively, to the extent a *prima facie case* is believed to be established, it is rebutted by the unexpected results of increased affinity.

For the above reasons, it is requested that the rejection under 35 U.S.C. § 103 be withdrawn.

Section 29

A copy of document AT is enclosed.

Summary

It is submitted that the remarks set forth above and the evidence sent herewith clearly show that the present application is in order for allowance which is hereby respectfully requested.

Respectfully submitted,

Doreen Yatko Trujillo

Doreen Yatko Trujillo
Registration No. 35,719

Date: September 18, 1995

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DOCKET NO.: CARP-0046 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Adair, et al.

Serial No.: **08/485,686** Group No.: **1806**

Filed: **June 7, 1995** Examiner: **Not Yet Assigned.**

For: **Humanised Antibodies**

CERTIFICATE OF FACSIMILE TRANSMISSION
I, Doreen Yatko Trujillo, Registration No. 35,719 certify that this correspondence is being facsimile transmitted to Examiner Ceeh at (703) 308-4242 at the U.S. Patent and Trademark Office., Washington, D.C. 20231.

On August 23, 1996
Doreen Yatko Trujillo
Doreen Yatko Trujillo, Reg. No. 35,719

Assistant Commissioner for Patents
Washington DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examination, please amend the above-identified application as follows:

In the Claims:

Please cancel claims 1-23.

Please add the following claims:

24. Antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues corresponding to the equivalent residues in a donor

Carter Exhibit 2015
Carter v. Adair
Interference No. 105,744

antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 100; and amino acid residues 23, 24, 49, 71, 73 and 78 at least are donor residues.

25. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 26 to 35, 50 to 65, and 95 to 102; and amino acid residues 23, 24 and 49 at least are donor residues.

26. An antibody according to claim 24 wherein one or more of residues 1, 3, 46, 48, 58, and 71 are additionally donor residues.

27. An antibody according to claim 25 wherein one or more of residues 1, 3, 46, 47, 48, 58, and 71 are additionally donor residues.

28. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat

Cont

numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 100; and amino acid residues 23, 24 and 49 at least are donor residues, provided that the antibody does not have affinity for the p55 chain of the human interleukin 2 receptor.

29. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 100, and amino acid residues 23, 24, 49, 71, 73 and 78 at least are donor residues, provided that the antibody does not have affinity for the p55 chain of the human interleukin 2 receptor.

30. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 26 to 35, 50 to 65, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues, provided that the antibody does not have affinity for the p55 chain of the human interleukin 2 receptor.

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31. An antibody according to claim 28 wherein one or more of residues 1, 3, 46, 47, 48, 58, and 71 are additionally donor residues.

32. An antibody according to claim 29 wherein one or more of residues 1, 3, 46, 47, 48, 58, and 71 are additionally donor residues.

33. An antibody according to claim 30 wherein one or more of residues 1, 3, 46, 47, 48, 58, and 71 are additionally donor residues.

34. An antibody molecule having affinity for a T-cell antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for a T-cell antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

35. An antibody molecule having affinity for a lymphokine and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for a lymphokine, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

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36. An antibody molecule having affinity for a growth factor and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for a growth factor, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

37. An antibody molecule having affinity for a stimulating factor and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for a stimulating factor, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

38. An antibody molecule having affinity for an interferon and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for an interferon, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

39. An antibody molecule having affinity for an adhesion molecule and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for an adhesion molecule, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

40. An antibody molecule having affinity for a hormone and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for a hormone, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

41. An antibody molecule having affinity for a cancer marker and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for a cancer marker, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

42. An antibody molecule having affinity for TNF-α and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for TNF-α, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

43. An antibody molecule having affinity for mucin and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for mucin, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

44. An antibody molecule having affinity for a receptor and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for a receptor, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

45. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in the donor murine antibody OKT3 having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

46. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in the donor murine antibody OKT4A having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

47. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in the donor murine antibody B72.3 having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor

residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

48. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in the donor murine antibody 61E71 having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

49. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in the donor murine antibody hTNF1 having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

50. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework

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residues, the remaining heavy chain residues, corresponding to the equivalent residues in the donor murine antibody hTNF3 having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

51. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in the donor murine antibody 101.4 having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

52. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in the donor murine antibody A5B7 having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 23, 24, and 49 at least are donor residues.

53. A therapeutic composition comprising an antibody molecule according to

claim 24 or claim 25 in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

54. A method of therapy comprising administering an effective amount of an antibody according to claim 24 or claim 25 to a human or animal subject.

55. A method of diagnosis comprising administering an effective amount of an antibody according to claim 24 or claim 25 to a human or animal subject.

REMARKS

The foregoing amendments are to remove improper multiple dependency and to otherwise advance prosecution. No new subject matter has been added. Support for the amendments can be found, *inter alia*, in claims 1-23 and Examples 1-5, of the application as originally filed. An early notification of allowance is earnestly requested.

Respectfully submitted,

Date: August 23, 1996

Doreen Yatko Trujillo
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5-1-97

DOCKET NO.: CARP-0057 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

3/B
D. Williams
9/11/97

In re application of:

Adair et al

Serial No.: Unassigned Group Art Unit: Unassigned

Filed: Herewith Examiner: Unassigned

For: HUMANIZED ANTIBODIES

I, Francis A. Paintin, Registration No. 19386 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On May 1, 1997
Francis A. Paintin

Assistant Commissioner
for Patents
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT AND REQUEST
FOR INTERFERENCE UNDER 37 CFR §1.607

Please amend the above-identified application as follows:

In the Specification:

At page 1, before line 1, insert the following:

--This application is a continuation of U.S. application Serial No.08/303,569, filed September 7, 1994, now U.S. Patent No. 5,859,205 which is a continuation of Serial No. 07/743,329, filed September 17, 1991, abandoned which is a U.S. national phase application stemming from PCT/GB90/02017, filed December 21, 1990, which PCT application claims priority benefit of GB national application Serial No. 89/28874.0, filed

B/#

December 21, 1989 in the United Kingdom, the entire content of each of said applications is incorporated by reference herein.--

Amend the above-identified specification in accordance with the enclosed copy of a preliminary amendment (dated 7/8/92) filed in applicants' Serial No. 07/743,329 application which enters the Sequence Listing as replacement pages 67-89, and renumbers original pages 67-70 as pages 90-93, respectively, and amends the specification to refer to said listing appropriately.

In the claims:

Cancel claim 1 without prejudice and enter the following claims 24-31 in this application:

--24. A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglogulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least 10^8 M^{-1}, wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside both the Kabat CDRs and the structural loop CDRs of the variable regions, wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, and each of said donor amino acids is adjacent to a CDR in the donor immunoglobulin sequence.

25. A humanized immunoglobulin according to claim 24 which specifically binds to an antigen with an affinity in the range 10^8-10^{12} M^{-1}.

26. A humanized immunoglobulin according to claim 24, wherein the antigen is an IL-2 receptor.

B2

27. A humanized immunoglobulin according to claim 24, wherein the donor immunoglobulin is the anti-CD4 T-cell receptor antibody.

Sub H2

28. A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglogulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an effective antigen binding affinity, wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside both the Kabat CDRs and the structural loop CDRs of the variable regions, wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, and each of said donor amino acids is adjacent to a CDR in the donor immunoglobulin sequence.

29. A humanized immunoglobulin according to claim 28 which specifically binds to an antigen with a binding affinity equivalent to that of a chimeric antibody formed from said donor immunoglobulin.

30. A humanized immunoglobulin according to claim 28, wherein the antigen is a human CD3 T-cell receptor.

31. A humanized immunoglobulin according to claim 28, wherein the donor immunoglobulin is the anti-CD3 T-cell receptor antibody.--

REMARKS

Applicants have entered claims 24-31 to request an interference in accordance with 37 CFR §1.607 as follows. It is noted that the Queen patent whose claims present the basis for an interference is classified in Class 424/133.1. MPEP §2306 suggests a transfer to the group where the patent is classified.

Compliance With 37 CFR §1.607(a)

(a) Identification of the Patent

Applicants request that an interference be declared between applicants' above-identified application and Queen et al., U.S. Patent No. 5,585,089 (hereinafter "the Queen patent"), issued December 17, 1996, a copy of which is enclosed herewith. Applicants have in claims 24-27 substantially copied claims 1, 5,

9 and 10 of the Queen patent. Applicants have fully complied with the requirements of 35 USC §135(b) in claiming substantially the same subject matter directed to the same invention as that claimed in the Queen patent prior to one year from the 12/17/96 date the Queen patent was granted.

(b) Presentation of a Proposed Count

Applicants present in Appendix A attached hereto the "Proposed Count." In compliance with 37 CFR §1.606, proposed Count 1 is broader than any of claims 1-4, the broadest claims in the Queen patent, and as broad as any one of claims 24-31 being entered into the instant application.

The proposed count contains disjunctive or alternative language to cover the claim terminology of the two parties. Such counts were expressly approved by the Board in *Hsing* v. *Myers*, 2 USPQ2d 1861 (Bd, Pat,. App. & Int. 1987). It is clear, however, that both alternatives are directed to the same invention as that claimed in the Queen patent.

For Queen's term, "Chothia CDRs", applicants' claims and the proposed count paragraph (b) use the alternative term "the structural loop CDRs of the variable regions." In the Queen patent (at col. 11, lines 38-44) it is stated that the light or heavy chain variable regions consist of a "framework" region interrupted by three "hypervariable regions, also called CDRs."

In Chothia et al., *J. Mol. Biol.*(1987) 197, pp.901-917,

the authors (at p. 904) define their "loops" as having "somewhat different" limits from those of the CDRs defined by Kabat et al.(1983). Chothia et al. (at page 904) describe six loops in the domains L1, L2, L3, H1, H2, and H3[1], and use the descriptive terms "hairpin loops" (Fig.1), "hairpin turns" (Table 2), and "hypervariable loops" (p.903) to describe their regions which Queen has chosen to call "Chothia CDRs". A copy of the Chothia et al. publication is enclosed.

(c) Identification of Claims Corresponding to the Count

Applicants identify all of the Queen patent claims 1-11 and applicant's claims 24-27 as corresponding to the Count and as being directed to the same patentable invention.

(d) Application of the Terms of Applicants' Disclosure to the Copied Claims

In attached Appendix B, applicants illustrate the representative support in their present application disclosure for the limitations of their claims 24-27, substantially copied from Queen claims 1, 5, 9 and 10. There is, of course, additional support in applicants' application omitted for the sake of brevity.

(e) Applicants' Effective Filing Date

Applicants' present application, being a Rule 60 continuation, has the identical specification and drawings as

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[1] In Fig. 1 of Chothia et al., these six domains are referred to as the "hypervariable regions."

that originally filed in U.S. application Serial No. 08/303.569, filed September 7, 1994, which is a U.S. national phase application stemming from PCT/GB-90/02017, filed December 21, 1990. The latter PCT application claimed priority benefit of GB national application Serial No. 89/28874.0, filed December 21, 1989. Enclosed is a copy of the GB application Serial No. 89/28874.0, a certified copy of which is on file in the aforesaid PCT/GB application.

In attached Appendix C is a diagram of support in applicants' 1989 GB application for each limitation of applicants' claims 28-31, which are also drawn to the same invention as proposed Count 1. Accordingly, applicants' effective filing date for their invention of Count 1 is 12/21/89, the filing date of their GB national application.

(f) Queen's Effective Filing Date

The Queen patent stems from U.S. Serial No. 08/477,728, filed June 7, 1995, which is a continuation of Serial No. 07/634,278, filed 12/19/90, which is a c-i-p of Serial No. 07/590,274, filed 9/28/90, and Serial No. 07/310,252, filed 2/13/89, which is a c-i-p of Serial No. 07/290,975, filed 12/28/88.

A careful study of Queen's 1988 and 1989 application disclosures reveals that that there is no disclosure therein for

certain critical limitations of the Queen patent claims and the proposed count, e.g., for the count limitation:

> ...said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside: (a) the Kabat and Chothia CDRs, or (b) both the Kabat CDRs and the structural loop CDRs of the variable regions,....

Neither of the Queen 1988 and 1989 applications contains any disclosure that teaches or suggests the requirement of amino acids from the donor Ig outside both the Kabat CDRs and structural loop (or Chothia) CDRs. This is a material limitation that was added to its claims by Queen to overcome the teachings of the prior art.[2]

The most that can be argued is that the 1988 and 1989 disclosures may be read to suggest that such amino acids are outside the Kabat CDRs; but nothing therein suggests that such amino acids also be outside the structural loop (or Chothia) CDRs. Thus, the absence of a disclosure of that presently claimed limitation in the earlier-filed Queen applications is clearly fatal to any attempt by Queen to claim priorty benefit thereof.

While applicants have been unable to locate a copy of the Queen application allegedly filed on 9/28/90 to evaluate its

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[2] In Queen's amendment of May, 31, 1996, at page 5, it was argued that the claims distinguish over the prior art because the immunoglobulins contain donor amino acids "outside the Kabat and Chothia CDRs."

disclosure, that application date is almost nine months later than the 12/21/89 filing date of applicants' GB application.

Queen should not be entitled to priority benefit of any application filed prior to 12/19/90, for the invention of Count 1 or its patent claims. Moreover, applicants do not concede that either the 12/19/90 application, or the application that matured into the Queen patent, contains an adequate disclosure of the invention of the proposed count. However, that issue need not be considered at this time.

Compliance With 37 CFR §1.608

Since applicants have the earlier effective filing date, there is no requirement for them to establish a prima facie case of earlier priority under §1.608.

The Requested Interference Should Be Declared

In applicants' parent application Serial No. 08/303,569, Queen's assignee, Protein Design Labs, Inc. ("PDL") has filed a Protest under 37 CFR §1.248. Therein, PDL specifically states (at page 2):

> [A]n interference analysis should be undertaken by the appropriate Examiner....

Thus, PDL acknowledges that there is interfering subject matter in the paties' respective applications. For that reason, applicants have filed the present application with claims specifically directed to the claimed ssubject matter of the Queen patent. This paper more accurately characterizes the effective

filing dates of the parties and shows that Queen would be the junior party of any interference declared hereon.

Applicants respectfully request that the proposed interference be promptly declared. MPEP §2307 states as follows:

> Examiners should note that 37 CFR 1.607 requires that examination of an application in which applicant seeks an interference with a patent "shall be conducted with special dispatch." See MPEP §708.01 (emphasis added herein).

Applicants wish to point out that in their efforts to provoke the interference, claims 1, 5, 9 and 10 of the Queen patent were substantially copied. Thus, most claim limitations are those that were examined and approved by the Examiner who allowed the Queen patent. Should the present examination involve rejections of applicants' claims that would have been equally applicable against the Queen claims, applicants respectfully note MPEP §2307.02, which requires the approval of the Group Director for such a rejection. Applicants are presumptively the prior inventors of the claimed subject matter and only desire an interference to prove that they are the actual prior inventors. Their opportunity to do so should not be unduly delayed.

Enclosed is a copy of an Information Disclosure Statement filed in applicants' parent Serial No. 08/303,569, filed 9/7/94, and Serial No. 07/743,929. Copies of the references are in said parent applications.

Please contact applicants' attorney, Francis A. Paintin, at 215-568 3100 if he can be of assistance in expediting this request.

Respectfully submitted,

Francis A. Paintin

Francis A. Paintin
Registration No. 19,386

Date: May 1, 1997

WOODCOCK WASHBURN KURTZ
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APPENDIX A

PROPOSED COUNT FOR INTERFERENCE

Count 1:

A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglogulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with:

(i) an effective antigen binding activity, or

(ii) an affinity constant of at least 10^7 M^{-1} and no greater than about four-fold that of the donor immunoglobulin,

wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside:

(a) the Kabat and Chothia CDRs, or

(b) both the Kabat CDRs and the structural loop CDRs of the variable regions,

wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, and each of said donor amino acids:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) contains an atom within a distance of 4 A^0 of a CDR in said humanized immunoglobulin .

APPENDIX B

Claim Limitation	Support in Adair Application
24. A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglogulin heavy and light chains	See page 1, lines 5-16, and page 7, line 32, through page 8, line 21.
which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least 10^8 M^{-1},	See page 11, lines 27-30.
wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside both the Kabat CDRs and the structural loop CDRs of the variable regions,	See page 6, lines 14-23, page 8, lines 13-16, and page 19, line 16, to page 20, line 15.
wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks,	See page 6, line 12, to page 7, line 5.

and each of said donor amino acids is adjacent to a CDR in the donor immunoglobulin sequence.	See page 11, lines 16-20, showing that homology is maximized between donor and acceptor sequences adjacent CDRs within acceptor framework. At page 6, lines 25-35, it is indicated that the heavy chain "framework comprises donor residues at at least one of positions 6, 23 and/or 24, 48 and/or 49...." In the heavy chain, Kabat CDR2 together with [Chothia] structural loop H2 extends from residues 50 to 65. Thus, residue 49 is immediately adjacent the beginning of this CDR2/H2 region. In Figs.3-4 residues marked with "N" to indicate near or adjacent a CDR (see p.38, l. 13.)
25. A humanized immunoglobulin according to claim 24 which specifically binds to an antigen with an affinity in the range 10^{8}-10^{12} M^{-1}.	Page 11, lines 27-30.
26. A humanized immunoglobulin according to claim 24, wherein the antigen is an IL-2 receptor.	Page 15, line 37, and page 16, line 2.
27. A humanized immunoglobulin according to claim 24, wherein the donor immunoglobulin is the anti-CD4 T-cell receptor antibody.	Page 53, Example 2.

APPENDIX C

Claim Limitation	Support in 1989 GB Application
28. A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglogulin heavy and light chains	See page 1, lines 1-2 and 10-20; page 5, lines 8, to page 6, line 4; , and page 8.
which humanized immunoglobulin specifically binds to an antigen with an effective antigen binding affinity'	See page 5, lines 1-7; page 22, lines 27-35, page 23, lines 5-9, page 24, lines 1-4; page 25, lines 27-33; page 26 last paragraph.
wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside both the Kabat CDRs and the structural loop CDRs of the variable regions,	See page 5, lines 1-7; page 26, last paragraph, to page 27, top paragraph.
wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks,	See page 5, line 8, to page 6, line 4: page 7, lines 5-20.

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and each of said donor amino acids is adjacent to a CDR in the donor immunoglobulin sequence.	See page 7, lines 11-14, showing that homology is maximized between donor and acceptor sequences adjacent CDRs within acceptor framework. At p.5, l. 9-16, reference is made to heavy chain "framework comprises donor at at least one of residues 6, 23 and/or 24, 48 and/or 49...." Residue 49 is immediately adjacent CDR2/H2 loop region. On Figs.20-21 residues marked "N" are near or adjacent a CDR.
29. A humanized immunoglobulin according to claim 28 which specifically binds to an antigen with a binding affinity as binding as a chimeric antibody formed from said donor immunoglobulin.	Page 23, lines 1-10; Fig. 29B.
30. A humanized immunoglobulin according to claim 28, wherein the antigen is a human CD3 T-cell receptor.	Page 11, lines 14-21. Page 17, lines 1-8; page 24, bottom paragraph.
31. A humanized immunoglobulin according to claim 28, wherein the donor immunoglobulin is the anti-CD3 T-cell receptor antibody.	Page 17, lines 1-8; page 24, bottom paragraph.

DOCKET NO.: CARP 0057 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

ADAIR ET AL.

For: HUMANIZED ANTIBODIES

Anticipated Classification of this application:

Class: 424, Subclass: 133.1

Prior Application
Examiner: D. ADAMS
Art Unit: 1816

"Express Mail" Label No. EM405876152US
Date of Deposit May 1, 1997

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Typed Name: Bob Lanzarotta

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington DC 20231

37 C.F.R. §1.60 TRANSMITTAL LETTER

Sir:

This is a request for filing a

(XX) Continuation ( ) Divisional

application under 37 CFR 1.60, of pending prior application Serial No.08/303,569, filed on September 7, 1994, which is a continuation of Serial No. 07/743,329, filed September 17, 1991.

1. (XX) Enclosed is a copy of prior application Serial No. 07/743,329, including the oath or declaration as originally filed.

I hereby verify that the attached papers comprise a true copy of the prior application Serial No. 07/743,329, as originally filed on September 17, 1991, and that no amendments referred to in the Oath or Declaration filed to complete the prior application introduced new matter therein.

The filing fee is calculated below on the basis of claims as filed in the prior application, less any claims cancelled or including any claims added by amendment listed below:

			SMALL ENTITY			OTHER THAN SMALL ENTITY	
For:	No. Filed	No. Extra	Rate	Fee	OR	Rate	Fee
BASIC FEE				$385	OR		$770
Total Claims	8 - 20 =		x $11=	$	OR	x $22=	$
Indep. Claims	2 - 3 =		x $40=	$	OR	x $80=	$
First Presentation Multiple Dependent Claims			+$130=	$	OR	+$260=	$
			TOTAL	$			$770

2. ( ) Verified Statement Claiming Small Entity Status is enclosed herewith.

3. ( ) Verified Statement Claiming Small Entity Status was filed in the parent case.

4. ( ) Please charge my Deposit Account No. 23-3050 in the amount of $_____. This sheet is attached in triplicate.

5. (XX) A check in the amount of $770.00 is attached. Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

6. (XX) The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 23-3050. This sheet is attached in triplicate.

   (XX) Any additional filing fees required under 37 CFR 1.16 including fees for presentation of extra claims.

   (XX) Any additional patent application processing fees under 37 CFR 1.17 and under 37 CFR 1.20(d).

7. (XX) The Commissioner is hereby authorized to charge payment of the following fees during the pendency of this application or credit any overpayment to Deposit Account No. 23-3050. This sheet is attached in triplicate.

(XX) Any patent application processing fees under 37 CFR 1.17 and under 37 CFR 1.20(d).

( ) The issue fee set in 37 CFR 1.18 at or before mailing of the Notice of Allowance, pursuant to 37 CFR 1.311(b).

(XX) Any filing fees under 37 CFR 1.16 including fees for presentation of extra claims.

8. (XX) Cancel in this application original claims 2-23 of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

9. (XX) Amend the specification as set forth in the accompanying preliminary amendment.

10. (XX) Formal drawings/photographs will be submitted when requested by the United States Patent and Trademark Office.

11. ( ) Please abandon said prior application as of the filing date accorded this application. A duplicate copy of this sheet is enclosed for filing in the prior application file. (May only be used if signed by person authorized by 37 CFR 1.138 and before payment of the base issue fee.)

12. (XX) Priority of GB application Serial No. 89/28874.0 filed on December 21, 1989 in United Kingdom (country) is claimed under 35 U.S.C. Section 119.

(XX) The certified copy has been filed in prior PCT application Serial No. PCT/GB90/02017, filed December 21, 1990.

13. (XX) The prior application is assigned of record to Celltech Limited.

14. ( ) Copy of the Assignment(s) of the invention and separate Form(s) 1595 for each Assignment will be submitted upon receipt of the Official Filing Receipt.

15. (XX) The power of attorney in the prior application is to Francis A. Paintin, Registration No. 19,386.

(XX) The power appears in the original papers in the prior application.

(XX) Since the associate power of attorney does not appear in the original papers, a copy of the associate power in the prior application is enclosed.

16. (XX) Address all future communications to:

Francis A. Paintin
WOODCOCK WASHBURN KURTZ MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103

17. (XX) A preliminary amendment is enclosed. Claims added by this amendment have been properly numbered consecutively beginning with the number next following the highest numbered original claim in the prior application.

18. ( ) A Petition for Extension of Time has been filed in the parent application, Serial No. _____ filed _____. A copy of the Petition for Extension of Time is enclosed.

19. (XX) Enclosed is a Statement to Support Filing and Submission of DNA/Amino Acid Sequences in Accordance with 37 CFR §§ 1.821 through 1.825 as filed in Serial No. 08/303,569.

(XX) Enclosed is a copy of a Letter of Reference to Computer Readable Form filed in Serial No. 08/303,569.

Date: May 1, 1997

Francis A. Paintin
Signature
Francis A. Paintin
Attorney of Record
Registration No. **19,386**

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DOCKET NO.: CARP-0046 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	:	John Robert Adair et al.
SERIAL NO.	:	08/485 686
FILED	:	JUNE 7, 1995
FOR	:	HUMANISED ANTIBODIES
GROUP ART UNIT	:	1816
EXAMINER	:	EVELYN RABIN Ph. D.

I, Doreen Yatko Trujillo, Registration No. 35,719 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On August 20, 1997

Doreen Yatko Trujillo

Doreen Yatko Trujillo, Esquire Reg. No. 35,719

Assistant Commissioner for Patents
Washington, DC 20231.

RESPONSE AND AMENDMENT

Dear Sir:

Pursuant to 37 C.F.R. § 1.115, Applicants submit the following in response to the Office Action dated February 20, 1997.

In the Claims:

Please cancel claims 24 to 55, without prejudice.

Please add the following claims.

--56. An antibody molecule having affinity for a predetermined antigen and

Carter Exhibit 2017
Carter v. Adair
Interference No. 105,744

comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarily determining regions (CDRS) , said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain at least residues 31 to 35, 50 to 65 and 95 to 102 (the CDRS) and at least residues 23, 24, 49, 71, 73 and 78 (in the framework regions) correspond to the equivalent residues in said donor antibody.

57. The antibody molecule of claim 56, wherein additionally residues 26 to 30 in said composite heavy chain correspond to the equivalent residues in said donor antibody.

58. The antibody molecule of claim 56, wherein additionally at least one of residues 6, 37, 48 and 94 in said composite heavy chain corresponds, to the equivalent residue in said donor antibody.

59. The antibody molecule of claim 57, wherein additionally at least one of residues 6, 37, 48 and 94 in said composite heavy chain corresponds to the equivalent residue in said donor antibody.

60. The antibody molecule of claim 58, wherein additionally at least one of

residues 2, 4, 25, 36, 39, 47, 93, 103, 104, 106 and 107 in said composite heavy chain corresponds to the equivalent residue in said donor antibody.

61. The antibody molecule of claim 59, wherein additionally at least one of residues 2, 4, 25, 36, 39, 47, 93, 103, 104, 106 and 107 in said composite heavy chain corresponds to the equivalent residue in said donor antibody.

62. The antibody molecule of claim 56, wherein said complementary light chain is a composite light chain having a variable domain including CDRS, said variable domain comprising predominantly human acceptor antibody light chain framework residues, the remaining light chain residues corresponding to the equivalent residues in said donor antibody, wherein, according to the Kabat numbering system, in said composite light chain at least residues 24 to 34, 50 to 56 and 69 to 97 (the CDRs) and at least residues 46, 48, 58 and 71 (in the framework regions) correspond to the equivalent residues in said donor antibody.

63. The antibody molecule of claim 62, wherein additionally at least one of residues 2, 4, 6, 35, 38, 44, 47, 49, 62, 64 to 69, 85, 87, 98, 99, 101 and 102 in said composite light chain corresponds to the equivalent residue in said donor antibody.

64. The antibody molecule of any one of claims 56, 57 or 62 which ~~is~~ has specificity ~~specific~~ for a T-cell antigen.

65. The antibody molecule of any one of claims 56, 57 or 62 which ~~is~~ has specificity ~~specific~~ for a lymphokine.

66. The antibody molecule of any one of claims 56, 57 or 62 which ~~is~~ has specificity ~~specific~~ for a growth factor.

67. The antibody molecule of any one of claims 56, 57 or 62 which ~~is~~ has specificity ~~specific~~ for interferon.

68. The antibody molecule of any one of claims 56, 57 or 62 which ~~is~~ has specificity ~~specific~~ for an adhesion molecule.

69. The antibody molecule of any one of claims 56, 57 or 62 which ~~is~~ has specificity ~~specific~~ for a hormone.

70. The antibody molecule of any one of claims 56, 57 or 62 which ~~is~~ has specificity ~~specific~~ for a cancer marker.

71. The antibody molecule of any one of claims 56, 57 or 62 which ~~is~~ has specificity ~~specific~~ for TNF-α.

72. The antibody molecule of any one of claims 56, 57 or 62 which ~~is~~ has ~~specific for~~ specificity for mucin.

73. A ~~therapeutic~~ composition comprising ~~an~~ the antibody of any one of claims 56, 57 or 62 in combination with a pharmaceutically acceptable carrier, diluent or excipient. --

Remarks

This paper is being filed in response to the Office Action dated February 20, 1997. A petition for a three-month extension of time, and the appropriate fee, accompanies this response.

Claims 24 to 55 were pending. Claims 24 to 55 have been canceled herein without prejudice, and replaced by the new claims 56 to 73.

Support for present claim 56 can be found, *inter alia,* on page 19, lines 24 and 25, of the application as filed which defines the extent of the heavy chain CDRs, and page 7, lines 1 to 3, which defines the preferred basic set of framework residues which correspond between the donor and humanized chains.

Support for claim 57 can be found, *inter alia*, on page 17, lines 11 to 13 of the application as filed, which defines the preferred extent of the "CDRs". This extension, in fact, merely adds the Chothia loop residues to CDR1 in the heavy chain (see also page 8, lines 17 to 22).

Claims 58 and 59 are based on page 7, lines 7 to 9 of the application as filed. Claims 60 and 61 are based on page 7, lines 9 to 14 of the application as filed.

Support for claim 62 can be found, *inter alia*, is based on page 17, lines 1-4 to 16, of

the application as filed, which defines the extent of the light chain CDRs, and page 18, line 21, which defines the preferred basic set of light chain framework residues which correspond between the donor and humanized chains.

Basis for claim 63 is found on page 18, lines 23 to 28 of the application as filed.

Basis for claims 64 to 72 is found on page 15, line 24 through page 16, line 3 and in the Examples of the application as filed. Basis for claim 73 is found on page 16, lines 5 to 8 of the application as filed.

In view of the foregoing amendments, and arguments which follow, Applicants hereby request withdrawal of all rejections upon reconsideration. To the extent the rejections of claims 24 to 55 may be applied to the present claims, Applicants submit the following.

Rejections Under 35 USC § 112

In light of the amendments to the claims, it is submitted that the points raised by the Examiner in Sections 3, 4 and 5 (35 U.S.C. § 112, first paragraph) are rendered moot.

As regards the objection set forth in the last two paragraphs of the Examiner's Section 5, Applicants respectfully submit that such a rejection is unfounded. It is first to be noted that the Examiner has made a number of sweeping assertions which are totally unsupported by any evidence, reference to the statute, or reference to legal precedent. In particular, the Examiner has provided no evidence of a technical nature.

It is to be pointed out that, by the priority date of the present application, a large number of monoclonal antibodies had been successfully used in therapy. In particular, the OKT3

antibody, which is the subject of one of the examples, had been in use since the early 1980's in the treatment of acute rejection episodes in liver transplant patients. Thus, by the priority date, it was well known how to make a therapeutic antibody composition.

As is shown in the present description, the humanized antibodies of the present invention have affinities similar to those of the monoclonal antibodies from which they are derived. It would therefore have been clear to the skilled person that a composition containing a humanized antibody would be very similar to a composition containing the monoclonal antibody. It is therefore submitted that a skilled person would have been able readily to produce a therapeutic composition containing a humanized antibody of the present invention.

It may be that the Examiner has doubts as to the efficacy of the humanized antibodies of the present invention. Again, however, the Examiner has provided no evidence to support any such doubts. The Applicants have a number of humanized antibodies according to the present invention in clinical trials at various stages. These trials have shown that the humanized antibodies are effective. It is therefore submitted that there is no basis for the Examiner's, rejection which should therefore be withdrawn.

It is believed that the point raised in Section 6 by the Examiner is now moot. In any event, it is submitted that it is not necessary to use the particular monoclonal antibodies recited by the Examiner. The procedure described in the application is a general procedure which can be applied to any donor antibody and to any acceptor antibody. The Applicants have shown that this protocol can be applied generally, and have successfully produced a number of humanized antibodies according to the invention. It is therefore submitted that the rejection should be withdrawn.

Rejection Under 35 USC § 102(e)

In her Section 8, the Examiner refers to U.S. Patent No. 5,530,101 issued to Queen et al. The Examiner indicates, almost as a footnote, that the Queen Patent apparently has an effective filing date of December 28, 1988. While this may be true, the disclosures of the earliest Queen applications do not support this rejection. Following on from the initial application filed on December 28, 1988, there was a continuation-in-part application (CIP) filed February 13, 1989. There was then a separate new application filed September 28, 1990. A further continuation-in-part application was filed December 19, 1990, which claims priority to the prior continuation-in-part application and he separate new application. The '101 patent granted on the last continuation-in-part application.

The present application has a priority date of December 21, 1989. Only the initial application and the first continuation-in-part application of the '101 patent were filed before Applicants' priority date. Therefore, in order for the Examiner to be able to show that the present claims lack novelty, it must be shown that any subject matter which may be relevant was disclosed in these two earliest Queen applications.[1] Applicants respectfully submit that the Examiner has not shown this.

Applicants have been able to study the two early Queen applications in connection with the application from which the present application is a continuation. This study shows that there is

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[1] Similarly, the most recently issued patent from the same family, U.S. Patent No. 5,585,089 issued to Queen et al. on December 17, 1996 (the "'089 patent") is to no avail. The claims specify that the changes be made "outside the Kabat *and* Chothia CDRs." (emphasis added) There was no mention of Chothia. CDRs in the two earliest Queen applications. Thus, the '089 patent is not entitled to a filing date of December 28, 1988.

considerably more subject matter in the granted '101 patent than in either of the two early Queen applications. As far as Applicants can tell, the only working example provided in the two early Queen applications is the anti-tac antibody which is referred to in Figures 1A and 1B of the '101 patent.

The Examiner will see from a study of Figure lB of the Queen Patent that residue 74 (according to the numbering in the Figure) is different between the mouse (top line) and human (bottom line) sequences. It is indicated in the Figure that the places where changes were made are indicated by double underlining. At residue 74, no change was made and so there is a clear difference between the humanized and mouse sequences. In Figure 1B, the sequences are numbered linearly and not according to the Kabat system. If the sequences are numbered according to the Kabat system, as specified in the present claim, linear residue 74 becomes Kabat residue 73. Since it is specified in present claim 56 that Kabat residue 73 should be identical between donor and acceptor sequences, it can be seen that the antibody of Figure 1 of the '101 Patent does not destroy the novelty of claim 56.

It is therefore submitted that there is no specific disclosure in the '101 patent entitled to the date of the two early Queen applications which destroys the novelty of present claim 56.

The general disclosure is equally unavailing. Looking first at the initial Queen application, it can be readily seen that it is not directed to a general process for humanizing antibodies. As is made clear from the introduction on pages 1 to 4 and the Summary of the Invention, the initial application is very specifically directed to the production of a humanized anti-tac antibody. Thus, there is absolutely no disclosure or suggestion of a claim to humanized antibodies in

general; nor is there any disclosure or suggestion to make the specific residues recited in the present claims donor.

Even if (which is denied) such a general teaching for humanizing anitbodies could be derived from the initial Queen application, it must be borne in mind that the teaching in the initial application is not enabling. It will be seen from pages 21 and 22 that there are disclosed three criteria for selecting framework residues outside the Kabat CDRs which can be considered for changing. One of these criteria is that the framework residues should be physically close to the antigen binding region. However, this criterion is so vague as to be meaningless. There is no description as to what "physically close" means. How close is close? How does, a skilled person build a model to determine whether a residue is close? What is the antigen binding region? It can thus be seen that it would be impossible for a skilled person to put this part of the teaching of the initial Queen application into effect.

The second Queen application has a slightly more general teaching. However, the general teaching is still not enabling for the invention recited therein, much less the present claims. It requires the skilled person to put into practice various criteria set out therein. One of these criteria is that residues a certain distance away from the antigen binding region should be identified. In order to identify these residues, it is necessary to build a molecular model of an antibody. Given the lack of detail in the Queen application, it is submitted that this would not have been possible.

By the date of filing of the continuation-in-part application, it was possible to build rough models of antibodies. However, these models could only be built using details which are not provided in this application. Even when such details were available, the models which were built

were not very accurate. The best accuracy was obtained for the main chain conformation of the framework regions, but even this was not very good. The modeled main chain conformations for the CDRs was poor. The results obtained for side chains, whether on framework or CDR residues, were not very accurate at all.

In the Queen applications, it is a requirement that a determination be made either of the physical closeness or of the distance between framework side chain atoms and CDR atoms. These are the two least accurate areas in any model. This clearly shows that it would not have been possible to put the teaching in the early Queen applications into effect in a reproducible manner, even using modern modeling programmes.

It is therefore submitted that there is no disclosure in either of the two early Queen applications, much less an enabling disclosure, of Applicants' invention. Thus, there can be no novelty-destroying disclosure therein.

Even if (which is denied) there were any enabling disclosure in the two Queen applications, it would still not be possible to obtain the subject matter of the present claims by following the teachings therein. Applicants have carried out their own modeling procedures using a current available modeling program. These results have shown that none of residues 23, 24, 71 and 73 in the heavy chain meet the criteria set out in the first Queen continuation-in-part application. A study of 39 solved X-ray crystal structures of antibodies homologous to the OKT3 antibody has shown that in NONE of these real (as opposed to modeled) structures does either residue 23 or residue 24 meet the distance criterion of the first Queen CIP application. Thus, as these residues would never be identified, there is no novelty-destroying disclosure in the two early Queen

applications.

If the Examiner requires, details of any of the studies the Applicants have made, can be submitted.

Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. §102(e) should be withdrawn.

Rejections Under 35 USC § 103

Regarding the Examiner's Section 10, it is hereby confirmed that the subject matter of the various claims was commonly owned at the time that the inventions covered by these claims were made.

In the remaining sections of the Office Action, the Examiner raises a number of obviousness rejections. These are all based on the Queen '101 patent which was discussed above in connection with novelty, discussion incorporated herein. It is submitted that the secondary references do not overcome the deficiencies of the '101 patent. The secondary references are relied upon for the specific antigen recitations in the dependent claims.

As stated above, even by the priority date of the present application, it was not possible to build accurate models of antibodies. The identification of residues which might be changed in the Queen applications is based on the use of molecular modeling. Since no accurate models could have been built, it would not have been possible to apply the teaching of the two early Queen applications to any antibody except the specific one referred to in the Queen applications. It has been shown above that this does not destroy the novelty of the present claims. Further, applying any teaching

derived from the Queen applications would still not produce anything falling within the present claims.

It should again be stressed that, in the CIP application, it is specified that residues within a certain distance of the CDR atoms should be selected as candidates for changing. Using modern molecular modeling techniques, it is possible to show that residues 23, 24, 71 and 73 in the heavy chain can never meet this distance criterion. As discussed previously, this is confirmed by studies of resolved structures for residues 23 and 24. Thus, even if it had been possible to build a molecular model at the priority date of the present application, doing so would not have identified the above four residues. It would not have been possible to produce anything falling within the present claims based on the teaching in these two early Queen applications.

None of the remaining references, or combination thereof, cited by the Examiner overcomes these deficiencies. Applicants respectfully submit that the rejections under 35 U.S.C. § 103(a) should be withdrawn.

Summary

It is submitted that the new claims submitted for the Examiner's attention are supported by the description as originally filed, are novel over any disclosure in the two early Queen applications, and are nonobvious over the '101 patent, whether taken alone or in combination with any other documents.

It is therefore submitted that the application is in condition for allowance, notice of which is hereby respectfully requested.

Respectfully requested

Date: August 20, 1997

Signature
Doreen Yatko Trujillo
Registration No. **35,719**

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DATE: January 28, 1998

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COVER MESSAGE: A proposed amendment to the previously allowed claims consistent with our discussions is attached. I look forward to speaking with you.

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PROPOSED CLAIMS

120. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues, corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 6, 23, 24, and 49 at least are donor residues, provided that said antibody is not the Queen et al. humanized anti-tac antibody.

121. The antibody molecule of claim 120, wherein amino acid residues 26 to 30 and 59 to 65 in said composite heavy chain are additionally donor residues.

122. The antibody molecule of claim 120, wherein amino acid residues 71, 73, and 78 in said composite heavy chain are additionally donor residues.

123. The antibody molecule of claim 120, wherein at least one of amino acid residues 1, 3, and 76 in said composite heavy chain are additionally donor residues.

124. The antibody molecule of claim 120, wherein at least one of amino acid residues 36, 94, 104, 106, and 107 in said composite heavy chain are additionally donor residues.

125. The antibody molecule of claim 124, wherein at least one of amino acid residues 2, 4, [6,] 38, 46, 67, and 69 in said composite heavy chain are additionally donor residues.

126. The antibody molecule of claim 120, wherein said complementary light chain is a composite light chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody light chain framework residues, the remaining light chain residues corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite light chain; said CDRs comprise donor residues at least at residues 24 to 34, 50 to 56, and 89 to 97; and amino acid residues 46, 48, 58, and 71 at least are donor residues.

127. The antibody molecule of claim 126, wherein amino acid residues 1, 3, 60 (if this residue can form a salt bridge with residue 54), and 70 (if this residue can form a salt bridge with residue 24) in said composite light chain are additionally donor residues.

DOCKET NO.: CARP-0032 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **John Robert Adair, Diljeet Singh Athwal, and John Spencer Emtage**

Serial No.: **08/303,569** Group Art Unit: **1816**

Filed: **9/07/94** Examiner: **L. Feisee**

For: **HUMANISED ANTIBODIES**

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450/II(N) Cancel 2/28/98

Certificate of Facsimile Transmission

I Doreen Yatko Trujillo, Registration No.: 35,719 hereby certify that this paper is being facsimile transmitted to Examiner Feisee at (703)305-7230 of the U.S. Patents and Trademark Office, Washington, D.C. 20231, on the date shown below

On February 23 1998

Doreen Yatko Trujillo

Doreen Yatko Trujillo, Registration Reg. No. 35,719

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Office of Publications
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Washington DC 20231

Dear Sir:

AMENDMENT PURSUANT TO 37 C.F.R. §1.312

Pursuant to 37 C.F.R. §1.312 (b), please amend the above-identified application as follows. A petition and appropriate fee accompanies this Amendment.

In the claims:

120. (Twice Amended) An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50

Carter Exhibit 2019
Carter v. Adair
Interference No. 105,744

to 58, and 95 to 102; and amino acid residues 6, 23, 24, and 49 at least are donor residues, provided that said antibody is not the humanized anti-tac antibody described in WO 90/07861.

125. (Amended) The antibody molecule of claim 124, wherein at least one of amino acid residues 2, 4, [6,] 38, 46, 67, and 69 in said composite heavy chain are additionally donor residues.

REMARKS

The foregoing amendments are being made to advance the present case to issuance. Although the issue fee had already been paid on December 4, 1996, issuance was delayed following the filing and subsequent entry of a Protest. These amendments are being submitted following the Examiner's consideration of the Protest, Applicants' response thereto, and a personal interview conducted with the Examiner on October 16, 1997. Thus, these amendments do not require additional search or examination, nor could they been submitted ealier. Support for the amendments can be found, *inter alia*, on page 5, line 10 through page 6, line 37, of the application as originally filed. The humanized anti-tac antibody of WO 90/07861 is therein described and distinguished from the present invention. The inclusion of residue 6 as a donor residue is also disclosed therein. As is clear from the foregoing, no new matter is added by these amendments. Applicants respectfully request that they be entered.

Respectfully submitted,

Doreen Yatko Trujillo

Date: February 23, 1998

Doreen Yatko Trujillo
Registration No. 35,719

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1642 1641

DOCKET NO.: CARP-0032 PATENT

Issue Batch No.: D80
Date of Notice
of Allowance : September 4, 1996
Serial No. : 08/303,569

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

John Robert Adair, Diljeet Singh Athwal, and John Spencer Emtage

Serial No.: **08/303,569** Group Art Unit: **1642**

Filed: **9/07/94** Examiner: **L. Feisee**

For: **HUMANISED ANTIBODIES**

Assistant Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

AMENDMENT PURSUANT TO 37 C.F.R. §1.312

Pursuant to 37 C.F.R. §1.312 (b), please amend the above-identified application as follows. A petition and the appropriate fee accompanies this Amendment.

In the specification:

Page 6, line 9, after "heavy chain", please insert -- SEQ ID NO:31 --.

Please replace pages 67-92 of the Sequence Listing with the attached substitute Sequence Listing, pages 67-93. Please renumber the pages thereafter accordingly.

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01 FC:122 130.00 OP

In the claims:

120. (Twice Amended) An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues corresponding to the

Carter Exhibit 2020
Carter v. Adair
Interference No. 105,744

equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 6, 23, 24, and 49 at least are donor residues, provided that said composite heavy chain does not comprise the amino acid sequence of SEQ ID NO: 31.

125. (Amended) The antibody molecule of claim 124, wherein at least one of amino acid residues 2, 4, [6,] 38, 46, 67, and 69 in said composite heavy chain are additionally donor residues.

REMARKS

The foregoing amendments are being made to advance the present case to issuance. Although the issue fee had already been paid on December 4, 1996, issuance was delayed following the filing and subsequent entry of a Protest in the above-identified application. In the Protest, U.S. Patent No. 5,585,089 issued to Queen et al. on December 17, 1996 was cited as relevant. These amendments are being submitted following the Examiner's consideration of the Protest, Applicants' response thereto, a personal interview conducted with the Examiner on October 16, 1997, and telephonic discussions and communications with the Examiner, as well as telephonic communications with Examiner Schwartz. These amendments do not require additional search or examination.

Support for the proviso in claim 120 can be found, *inter alia*, on page 5, line 10 through page 6, line 37, of the application as originally filed. The heavy chain variable region of the humanized anti-tac antibody of WO 90/07861 is therein described and distinguished from the present invention. The heavy chain variable region of the humanized anti-tac antibody of WO 90/07861 was, thus, incorporated by reference. The inherent amino acid sequence of the heavy chain variable region of the humanized anti-tac antibody of WO 90/07861 was, thus, also incorporated by reference. In view of its recitation in claim 120, the amino acid sequence of the heavy chain variable region of the humanized anti-tac antibody of WO 90/07861 is presumed essential. Accordingly, Applicants have amended the specification to include the sequence of

the heavy chain variable region of the humanized anti-tac antibody described in WO 90/07861. The sequence is included as SEQ ID NO: 31 of the substitute Sequence Listing. A paper and computer-readable copy of the substitute Sequence Listing, and accompanying papers, are included herein. A Declaration by the undersigned that the amendatory material consists of the same material incorporated by reference is included pursuant to M.P.E.P. 608.01(p). Applicants have also corrected typographical errors in the sequence listing inadvertently introduced in the substitute Sequence Listing previously submitted on December 4, 1996.

Support for the recitation of residue 6 as a donor residue can be found, *inter alia*, on page 6, line 35, of the application as filed.

No new matter is added by any of the foregoing.

Applicants request that the foregoing amendments be entered and that, upon their entry, the application be allowed to issue. Pursuant to M.P.E.P. § 1309, Applicants request that the application be tagged to ensure appropriate printing priority in the publishing division. This application is at least entitled to category (2) priority as listed in M.P.E.P. § 1309.

If anything remains outstanding, the Examiner is requested to contact the undersigned at (215) 564-8352.

Respectfully submitted,

Doreen Yatko Trujillo

Date: July 13, 1998

Doreen Yatko Trujillo
Registration No. **35,719**

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DATE: September 29, 1998

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ALLOWED CLAIMS

120. An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody heavy chain framework residues, the remaining heavy chain residues corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain: said CDRs comprise donor residues at least at residues 31 to 35, 50 to 58, and 95 to 102; and amino acid residues 6, 23, 24, and 49 at least are donor residues, provided that said composite heavy chain does not comprise the amino acid sequence of SEQ ID NO: 31.

121. The antibody molecule of claim 120, wherein amino acid residues 26 to 30 and 59 to 65 in said composite heavy chain are additionally donor residues.

122. The antibody molecule of claim 120, wherein amino acid residues 71, 73, and 78 in said composite heavy chain are additionally donor residues.

123. The antibody molecule of claim 120, wherein at least one of amino acid residues 1, 3, and 76 in said composite heavy chain are additionally donor residues.

124. The antibody molecule of claim 120, wherein at least one of amino acid residues 36, 94, 104, 106, and 107 in said composite heavy chain are additionally donor residues.

125. The antibody molecule of claim 124, wherein at least one of amino acid residues 2, 4, 38, 46, 67, and 69 in said composite heavy chain are additionally donor residues.

126. The antibody molecule of claim 120, wherein said complementary light chain is a composite light chain having a variable domain including complementarity determining regions (CDRs), said variable domain comprising predominantly human acceptor antibody light chain framework residues, the remaining light chain residues corresponding to the equivalent residues in a donor antibody having affinity for said predetermined antigen, wherein, according to the Kabat numbering system, in said composite light chain; said CDRs comprise donor residues at least at residues 24 to 34, 50 to 56, and 89 to 97; and amino acid residues 46, 48, 58, and 71 at least are donor residues.

127. The antibody molecule of claim 126, wherein amino acid residues 1, 3, 60 (if this residue can form a salt bridge with residue 54), and 70 (if this residue can form a salt bridge with residue 24) in said composite light chain are additionally donor residues.

LH 11-20-98 Ana Bandt 14/F

DOCKET NO.: CARP-0057 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Adair et al

Serial No.: 08/846,658 Group Art Unit: 1642

Filed: May 1, 1997 Examiner: J. Reeves

For: HUMANIZED ANTIBODIES

I, Francis A. Paintin, Registration No. 19386 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On Nov. 5, 1998

Francis A. Paintin

Assistant Commissioner
for Patents
Washington, D.C. 20231

Dear Sir:

FOURTH PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

In the claims:

Please enter the following claims 32-48 in this application:

32. First and second polynucleotides respectively encoding heavy and light chain variable regions of a humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chain frameworks, which humanized immunoglobulin

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specifically binds to an antigen with an affinity constant of at least about $10^8\ M^{-1}$ and no greater than about four-fold that of the donor immunoglobulin, wherein the sequence of the humanized immunoglobulin heavy chain variable region framework is at least 65% identical to the sequence of the donor immunoglobulin heavy chain variable region framework and comprises at least 70 amino acid residues identical to those in the acceptor human immunoglobulin heavy chain variable region framework.

33. A vector comprising first and second polynucleotides according to claim 32.

34. First and second polynucleotides respectively encoding heavy and light chain variable regions of a humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chain frameworks, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least about $10^8\ M^{-1}$ and no greater than about four-fold that of the donor immunoglobulin, wherein the sequence of the acceptor immunoglobulin heavy chain variable region framework is a

consensus sequence of human immunoglobulin heavy chain variable region frameworks.

35. First and second polynucleotides respectively encoding heavy and light chain variable regions of a humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least about $10^8\ M^{-1}$ and no greater than about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin heavy chain comprises one or more amino acids from the donor immunoglobulin heavy chain framework outside the Kabat and Chothia CDRs, wherein the donor amino acids substitute for corresponding amino acids in the acceptor immunoglobulin heavy chain framework, and each of these said donor amino acids:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) contains an atom within a distance of 6 ANGSTROM of a CDR in said humanized immunoglobulin.

36. First and second polynucleotides respectively encoding heavy and light chain variable regions of a humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of a least about $10^8\ M^{-1}$ and no greater than about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin heavy chain comprises one or more amino acids from the donor immunoglobulin heavy chain framework outside the Kabat and Chothia CDRs that substitute for the corresponding amino acids in the acceptor immunoglobulin heavy chain framework, wherein each of these said donor amino acids:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) is capable of interacting with amino acids in the CDRs, or

(III) is typical at its position for human immunoglobulin sequences, and the substituted amino acid in the acceptor is rare at its position for human immunoglobulin sequences.

37. A cell line transfected with a vector according to claim 33.

38. First and second polynucleotides respectively encoding heavy and light chain variable regions of a humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chain frameworks, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold of that of the donor immunoglobulin, wherein the sequence of the humanized immunoglobulin heavy chain variable region framework is at least 65% identical to the sequence of the donor immunoglobulin heavy chain variable region framework and comprises at least 70 amino acid residues identical to those in the acceptor human immunoglobulin heavy chain variable region framework.

39. First and second polynucleotides respectively encoding heavy and light chain variable regions of a humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chain frameworks, which humanized immunoglobulin specifically binds to an antigen with an affinity constant within about four-fold of that of the donor