IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Shmuel Cabilly, Herbert L. Heyneker, William E. Holmes, Arthur D. Riggs and Ronald B. Wetzel

Patent No.: 6,331,415
Issued: 18 December 2001
Assignee: Genentech, Inc. and City of Hope
TITLE: METHODS OF PRODUCING IMMUNOGLOBULINS, VECTORS AND TRANSFORMED HOST CELLS FOR USE THEREIN

Docket No.: 469201-743

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REQUEST FOR REEXAMINATION
UNDER 35 U.S.C. §302 AND 37 C.F.R. 1.510

Sir:

Reexamination of U.S. Patent No. 6,331,415 (hereafter, Cabilly II), a copy of which is attached hereto as an Appendix E, is requested pursuant to 35 U.S.C. §302 and 37 C.F.R. §1.501, based on the prior art cited in the accompanying Form 1449 and

on U.S. Patent No. 4,816,567, copies of all of which references are attached hereto. In compliance with 37 C.F.R. §1.33(c) and 37 C.F.R. §1.510(b)(5), the present Request for Reexamination is being served on the Attorney of Record for U.S. Patent No. 6,331,415 and on Co-Assignee City of Hope, Duarte, CA.

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I. CLAIMS FOR WHICH REEXAMINATION IS REQUESTED

U.S. Patent No. 6,331,415 (Cabilly II) contains claims 1-36. Reexamination is herein being requested specifically for claims 1-36. This request for reexamination is based on the ground of double patenting, more specifically, obviousness-type double patenting. The claims of Cabilly II are unpatentable for obviousness-type double patenting over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly I) in view of the prior art attached to this Request.

II. A SUBSTANTIAL NEW QUESTION OF PATENTABILITY EXISTS

A. PRIOR REQUEST

A request, by a third party, for re-examination of the claims of Cabilly II based on obviousness-type double patenting of Cabilly II over Cabilly I has already been granted (see Reexamination Control No. 90/007,542), resulting in rejection of claims 1-36 of Cabilly II for obviousness-type double patenting over the claims of Cabilly I. The owner filed a response on November 25, 2005.

B. THIS CURRENT REQUEST

Although this current request also requests reexamination based on obviousness-type double patenting over Cabilly I, this current request relies on certain prior art that was not employed in the initial request for reexamination or the rejection based thereon; namely Deacon ("Antibody Synthesis in *Xenopus* Oocytes with Messenger Ribonucleic Acid from Immunized Rats," Biochemical Society Transactions, 4:818-20 (1976)); Dallas (WO 82/03088); 1981 Valle (Nature, Vol. 291, pp. 338-340 (28 May 1981)); 1982 Valle (Nature, Vol. 300, pp. 71-74 (4 November 1982)), and Ochi (Nature, Vol. 302, pp. 340-342 (24 March 1983).

Deacon, 1981 Valle and 1982 Valle each disclose that exogenous immunoglobulin heavy and light chains, when expressed in a single cell, are assembled into an immunoglobulin. (See Section III A of this current request)

In particular, in this current request, the claims of Cabilly I are combined with Deacon and/or 1981 Valle and/or 1982 Valle and/or Ochi, plus other references for certain dependent claims. Such combination demonstrates that the claims of Cabilly II are unpatentable based on obviousness type of double patenting.

In Reexamination Control No. 90/007,542 (hereinafter "Pending Reexamination"), in which the claims of Cabilly II were rejected over the claims of Cabilly I based on obviousness-type double patenting, the owner has argued in the response filed on November 25, 2005 (the "Owners' Response") that the rejection is improper in that neither the claims of Cabilly I nor any of the other prior art relied on by the Examiner in such rejections suggest expressing two exogenous immunoglobulin chains in a single cell to produce an immunoglobulin. For example, the Owners' Response states as follows:

> Thus, the Office may not cite the '567 patent [Cabilly I] claims to suggest that the '567 patent claims "enable" the production of one or more immunoglobulin chains, or that they "suggest" the production of two immunoglobulin chains in a single host cell. Rather, such evidence must come from the prior art used in conjunction with the patent claims at issue. As explained above, Axel [U.S. Patent 4,399,216] provides no such evidence. [Page 38, first full paragraph, lines 5-9] [1]

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[1] To the extent that the Owners' Response asserts that Axel does not suggest expressing two immunoglobulin chains in a single cell, such assertion is wrong. Claim 7 of Axel defines that DNA I codes for an antibody whereby the DNA I expressed in the cell, by necessity, encodes heavy and light chains. Moreover, the Abstract of Axel discloses that the DNA coding for the desired protein includes "a gene or genes (emphasis added)", thereby further indicating that the DNA I disclosed in Axel can encode more than one protein. Although Axel does not include a specific example with respect to immunoglobulin expression, it is incorrect to argue that Axel does not suggest that DNA I can encode two proteins and that Axel does not suggest that such two proteins can be the proteins that form an immunoglobulin (heavy chain and light chain).

Further:

> The claimed invention [Cabilly II] require[s] expression of recombinant DNA sequences encoding exogenous heavy and exogenous light chain polypeptides. As Dr. Harris points out in his declaration at paragraph 36:
>
> > In my view, the Rice paper does not address the question of whether exogenous light and heavy chain polypeptides, if expressed by a transformed host cell, will be assembled into an "intact" immunoglobulin molecule. Instead, what Rice shows is that it is possible to express an exogenous light chain polypeptide in a particular mature B-cell subclone that was already expressing an endogenous heavy chain and had lost its previous ability to produce endogenous light chain.
>
> Thus, contrary to the Examiner's suggestions, the Rice paper does not even address the question of expressing exogenous heavy and light chain genes in a single host cell. The Examiner also mischaracterizes the actual observations in the Rice paper regarding the formation of immunoglobulins from the 81A-2 cell line.[2] [Page 42, lines 1-14]

Although such arguments do not establish that the rejection in the Pending Reexamination is incorrect (see Footnote 1 and the Declaration of Dr. Baltimore (Appendix D), a co-author of Rice and a Nobel Laureate, filed herewith to explain the teachings of Rice and to support the present re-examination request as to certain dependent claims of Cabilly II), each of Deacon, 1981 Valle and 1982 Valle remedy the alleged deficiencies asserted by the Owner in response to the rejection in the Pending

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[2] Owners' Response and accompanying Declarations correctly note that the immunoglobulin produced in Rice was not demonstrated to be functional. However, they ignore the fact that (i) the independent claims of Cabilly II do not recite that the immunoglobulin is "functional;" (ii) Rice teaches one skilled in the art that an immunoglobulin light chain that is exogenously produced in a cell assembles with a heavy chain produced in the cell to produce an immunoglobulin; and (iii) such teaching by Rice would suggest to one skilled in the art that the expression of an exogenous heavy chain and an exogenous light chain as disclosed by the claims of Cabilly I, if expressed in a single cell, would be expected to assemble into an immunoglobulin, even if the chains are from different immunoglobulins with different specificities. In this respect, see the accompanying Declaration of Dr. Baltimore (Appendix D).

Reexamination. Each of such references discloses the production of two exogenous immunoglobulin chains in a single host cell to produce an assembled immunoglobulin. Moreover, each of Deacon and 1982 Valle tested the assembled immunoglobulin, and such testing demonstrated that the immunoglobulin is functional; i.e., it binds to its antigen.

Since each of Deacon, 1981 Valle and 1982 Valle teach one skilled in the art to produce two exogenous immunoglobulin chains in a single cell and that such chains are assembled into an immunoglobulin, it would have been obvious to one of ordinary skill to perform the expression of heavy and light chains as set forth in the claims of Cabilly I in a single cell to produce an assembled immunoglobulin.

This combination presents a substantial new question as to patentability in that such a combination was not applied during the prosecution that led to the granting of Cabilly II or in the Pending Reexamination.

Dallas discloses expressing two different proteins (in addition to a selectable marker) in a single cell by independently expressing each of the proteins from DNA encoding such proteins using two different vectors or by independently expressing the two proteins from such DNA in the same vector.

This teaching of Dallas in combination with the claims of Cabilly I is relevant to the claims of Cabilly II that are limited to a vector that includes DNA encoding both the immunoglobulin heavy chain and the immunoglobulin light chain.

This combination presents a substantial new question as to patentability in that such a combination was not applied during prosecution that led to the granting of Cabilly II or in the Pending Reexamination.

There is also another substantial new question of patentability based on the claims of Cabilly I in combination with Ochi.

Ochi discloses that an exogenous light immunoglobulin chain that is produced in the same mammalian cell as a heavy immunoglobulin chain assembles into a functional immunoglobulin that is secreted from the cell as a functional immunoglobulin. Based on such teachings of Ochi, one skilled in the art would have found it to be obvious to express the heavy and light chains specified in the claims of Cabilly I in a single cell to produce a functional antibody. Such combination demonstrates that the Claims of Cabilly II are unpatentable based on obviousness-type double patenting.

Such a combination presents a substantial new question of patentability in that such combination was not applied during prosecution or during the Pending Reexamination.

Appendix A, attached hereto, contains a complete set of the claims of Cabilly II. Appendix B contains a complete set of the claims of Cabilly I.

C. CABILLY II IS NOT SHIELDED BY 35 U.S.C. 121

35 U.S.C. 121 states in part as follows:

> A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

As observed by the Federal Circuit, "[w]hen the PTO requires an applicant to withdraw claims to a patentably distinct invention (a restriction requirement), §121 shields those withdrawn claims in a later divisional application against rejection over a

patent that issues from the original application." *Geneva Pharmaceuticals Inc. v. GlaxoSmithKline,* 349 F.3d 1373, 1379, 68 USPQ2d 1865, 1869 (Fed. Cir. 2003)

The courts have held that a patentee is entitled to invoke this statutory prohibition only if the divisional application was filed as a result of a restriction requirement that caused the patentee to pursue separate applications for the issued and subsequent patent and is consonant with the restriction requirement. *Bristol-Myers Squibb Co. v. Pharmachemie B.V.,* 361 F.3d 1343, 70 USPQ2d 1097 (Fed. Cir. 2004).

In order to claim the protection of §121, this section requires "that the earlier application must contain formally entered claims that are restricted and removed, and that claims to the second invention reappear in a separate divisional application after the restriction. The text of §121 does not suggest that the original application merely needs to provide some support for claims that are first entered formally in the later divisional application." *Geneva Pharmaceuticals Inc.,* 349 F.3d at 1379, 68 USPQ2d at 1870.

No restriction requirement was entered by the examiner during prosecution of the application maturing into Cabilly I. Since no restriction was applied in Cabilly I, the inventors of Cabilly I voluntarily filed the application that matured into Cabilly II, whereby the "shield" of 35 USC § 121 is not available with respect to the claims of Cabilly II.[3]

Because of the absence of any restriction requirement during prosecution of Cabilly I, a 35 U.S.C. §121 "shield" is not available in Cabilly II to protect the claims of Cabilly II from being held invalid for obviousness-type double patenting over the claims of Cabilly I.

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[3] Although there was a restriction requirement in Cabilly II, such restriction requirement may only be asserted as a "shield" under 35 USC § 121 with respect to a later application that is filed as a result of such restriction requirement, e.g. Geneva Pharmaceuticals v. GlaxoSmithKline, supra.

D. THE PTO POSITION DURING PROSECUTION IS NOT RELEVANT TO THIS REQUEST.

As indicated in Part C above, 35 USC 121 does not bar the PTO from considering the issue of obviousness-type of double patenting.

The Owners Response (for example, pages 8-14) asserts that the issue of double patenting, in effect, was previously decided by the PTO and, therefore, the Examiner should not reconsider the issue.

However, the basis of the Pending Reexamination and this present reexamination request is the raising of new issues of patentability. Therefore, there is no merit to the Owners' position because both requests for reexamination are based on arguments that were not previously presented to the PTO. In particular, the present reexamination sets forth that the expression of the heavy and light chains of the claims of Cabilly I in a single cell is an obvious modification of such claims based on prior art that was not previously employed to support such an argument. In the absence of the shield of 35 USC 121 (there is no shield in the instant case), the PTO is not precluded from reaching a conclusion that the claims of Cabilly II are not separately patentable based on the arguments and the prior art of record in the applicable reexamination proceeding.[4]

[4] It is noted that the Owners Response in this respect is particularly misleading in that in the Pending Reexamination the owners did not challenge that the reexamination request presented a substantial new question. Since the request was granted, by definition, new issues were presented. The Owners had every opportunity to respond to the Prior Request before it was granted, but chose not to do so. As a result, the owners should not be permitted to argue that the issue of double patenting was previously decided and, therefore, the PTO cannot reexamine the claims of Cabilly II and conclude that such claims are unpatentable based on obviousness-type double patenting.

E. OBVIOUSNESS-TYPE DOUBLE PATENTING

Obviousness-type double patenting is "a judicially-created doctrine grounded in public policy rather than statute and primarily intended to prevent prolongation of monopoly by prohibiting claims in a second patent not patentably distinguishing from claims of a first patent." *In re Thorington*, 418 F.2d 528, 534, 163 USPQ 644, 648 (CCPA 1969). The legal rationale for this doctrine was made clear by the Federal Circuit in *Geneva Pharmaceuticals Inc. v. GlaxoSmithKline,* 349 F.3d 1377, 1378, 68 USPQ2d 1865, 1868 (Fed. Cir. 2003), where it noted that 35 U.S.C. 101 "only prohibits a second patent on subject matter identical to an earlier patent. *Id.* Thus, applicants can evade this statutory requirement by drafting claims that vary slightly from the earlier patent." Accordingly, obviousness-type double patenting "prevents an applicant from extending patent protection for an invention beyond the statutory term by claiming a slight variant." [*Geneva*, 349 F.3d at 1378, 68 USPQ2d at 1869]

Obviousness-type double patenting extends the doctrine of double patenting so as to bar obvious variants of what has already been patented. *In re Berg*, 140 F.3d 1428, 1432, 46 USPQ 2d 1226, 1229 (Fed. Cir. 1998). Such double patenting of the obviousness-type thereby serves to preclude issuance of a patent where there is no "patentable difference" or no "patentable distinction" between the two claims. *In re Goodman*, 11 F.3d 1046, 1052, 29 USPQ2d 2010, 2015 (Fed. Cir. 1993). As a result, the public is free to practice obvious variations of the first patented invention after expiration of the earlier patent. *In re Longi*, 759 F.2d 887, 892, 225 USPQ 645, 648 (Fed. Cir. 1985). " '[O]bviousness-type' double patenting" is a judge-made doctrine that prevents an unjustified extension of the patent rights beyond the statutory time limit. It requires rejection of an application claim when the claimed subject matter is *not patentably distinct* from the subject matter claimed in a commonly owned patent when the issuance of a second patent would provide an unjustified extension of the term of the right to exclude granted by a patent." [emphasis in original] *Ex parte Davis*, 56 USPQ2d 1434, 1435-36 (Bd. Pat. App. & Int. 2000).

"Obviousness-type double patenting is a question of law." *In re Goodman*, 11 F.3d at 1052, 29 USPQ2d at 2015.

F. OBVIOUS-TYPE DOUBLE-PATENTING IN REEXAMINATION

"A double patenting issue may raise a substantial new question of patentability of a claim of a patent, and thus be addressed in a reexamination proceeding." (MPEP §804(I)(D)). "[T]he issue of double patenting is appropriate for consideration in reexamination, both as a basis for ordering reexamination and during subsequent examination on the merits. The issue of double patenting is to be considered by the examiner when making the decision on the request for reexamination." (MPEP §2258(I)(D)) Furthermore, "The issue of double patenting is also to be considered during the examination stage of a reexamination proceeding. In the examination stage, the examiner should determine whether a rejection based on double patenting is appropriate." (Ibid.) Obviousness-type "[d]ouble patenting rejections are analogous to rejections under 35 U.S.C. 103 and depend on the presence of a prior patent as the basis for the rejection." (*Ex parte Obiaya,* 1985 WL 71916, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985), and at MPEP §2258(I)(D))

In reaching a conclusion of obviousness-type double patenting, the usual obviousness grounds of rejection as discussed in G*raham v. John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1966) are relevant. The MPEP §804(II)(B)(1) prescribes that "the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection:"

III. <u>This Request Is Based on Obviousness-Type Double Patenting</u>

A. <u>The Prior Art Relied on by Requestor</u>

1. Cabilly I (U.S. Patent No. 4,816,567)

The claims of Cabilly I disclose: (i) preparing a DNA sequence encoding a specific type of immunoglobulin light chain (a chimeric light chain) or heavy chain (a chimeric heavy chain); (ii) inserting the DNA sequence into a vector linked to a promoter; (iii) transforming a host cell with such vector; (iv) culturing the host cell; and (v) recovering such heavy or light chain from the host cell culture.

Since the heavy chain or light chain is recovered from the host cell culture, the heavy or light chain was expressed in the cell. As a result, the claims of Cabilly I teach the independent expression of a chimeric heavy chain or chimeric light chain in a host cell, and a vector that contains such chimeric heavy chain or chimeric light chain.

2. Deacon ("Antibody Synthesis in *Xenopus* Oocytes with Messenger Ribonucleic Acid from Immunized Rats," Biochemical Society Transactions, 4:818-20 (1976))

Deacon modified oocytes by injecting mRNA encoding heavy and light immunoglobulin chains which assembled into an immunoglobulin of defined specificity.

Deacon immunized adult rats with an antigen (some with hemocyanin and some with ferritin) and subsequently extracted RNA from the spleens of these rats. The total RNA fraction was subjected to cellulose fractionation to collect mRNA (which sticks to the cellulose because of its polyA tail) and the mRNA fraction was used for injection into *Xenopus* oocytes. Each of 40 oocytes was injected with RNA and ^{35}S-methionine (the latter would be incorporated as a radiolabel into any newly synthesized proteins) and incubated for 24 hours in L15 medium. The oocytes were then homogenized, centrifuged and the supernatants collected for analysis. (See Page 818)

Deacon used rat immunoglobulin antiserum to precipitate proteins from the supernatant for analysis by SDS-PAGE (polyacrylamide gel electrophoresis), which showed the presence of tetrameric immunoglobulin molecules as well as free heavy and

light chains. The specificity of the immunoglobulin was demonstrated by passing supernatant from the oocytes through a Sepharose-coupled antigen column (containing either hemocyanin or ferritin). Material that bound to the column was subsequently eluted with buffer, then assayed for protein and radiolabel. Peak fractions were pooled and analyzed by SDS-PAGE. These showed the presence of material with mobilities similar to those of marker heavy and light chains run in parallel gels. (see Page 819 and Figure 2)

Deacon concluded (at page 820, lines 1-5) that "mRNA from hyperimmunized rats, when injected into oocytes, is translated into heavy and light chains" and that "in the oocytes, heavy and light chains can be assembled into immunoglobulin molecules, which can behave as antibodies directed against antigen."

Deacon, therefore, discloses a process in which a cell that does not normally produce an immunoglobulin is modified with genetic material that encodes the heavy and light chains of an immunoglobulin and in which the heavy and light chains expressed in such cell assemble into a functional immunoglobulin.

3. 1982 Valle, Anti-Ovalbumin monoclonal antibodies interact with their antigen in internal membranes of *Xenopus* oocytes, Nature, Vol. 300, pp. 71-74 (4 November 1982).

1982 Valle expressed a functional immunoglobulin from heterologous mRNA introduced into oocytes.

Valle prepared two hybridomas (dubbed 7/2 and 7/4, both of IgG_1 type) by fusing spleen cells (from mice immunized with ovalbumin) with myeloma cells. Binding studies showed that these hybridomas recognized different single antigenic determinants on the ovalbumin. Immunoprecipitates of these immunoglobulins had the same electrophoretic mobility as analogous immunoprecipitates from oocytes injected with the hybridoma mRNAs. (see page 71, column 2, ¶2 and ¶3, lines 1-4)

In the experiment depicted in Figure 1, 1982 Valle disclosed exogenous expression of the heavy and light chains of immunoglobulin 7/2 in oocytes by use of mRNA. 1982 Valle demonstrated that the exogenously expressed chains assembled into an immunoglobulin that was immunologically functional in that it bound to ovalbumin. (See Figure 1C, lane 1). 1982 Valle performed the same successful experiment with immunoglobulin 3/4 (See Figure 1C, lane 2).

Accordingly, Deacon and 1982 Valle teach one skilled in the art at least the following:

(a) An immunoglobulin can be produced in a cell that does not normally produce such immunoglobulin by expressing in a single cell the proteins that form such immunoglobulin (the heavy chain and the light chain);

(b) The exogenous expression of the two immunoglobulin chains in a single cell produces an assembled immunoglobulin;

(c) The immunoglobulin expressed in such cell is immunologically functional in that it binds to the antigen against which the immunoglobulin was originally produced;

(d) The production of such an immunoglobulin does not require any changes to the cell other than providing the genetic material that encodes the immunoglobulin heavy chain and the immunoglobulin light chain followed by expression of such two chains from such genetic material;

(e) No special techniques are required in order to assemble the expressed two chains into a functional immunoglobulin.

4. 1981 Valle, Synthesis and secretio of mouse immunoglobulin chains in *Xenopus* oocytes, Nature, Vol. 291, pp. 338-340 (28 May 1981).

1981 Valle discloses the production and secretion of tetrameric immunoglobulin molecules from *Xenopus* oocytes. In one of the disclosed experiments, 1981 Valle injected X63 mRNA (from a P3/X63 cell line producing MPOC 21 immunoglobulin, consisting of a gamma 1 heavy chain and a kappa light chain) into *Xenopus* oocytes, incubated the cells, collected extracellular medium and analyzed this by non-reducing gels to show the formation of tetrameric immunoglobulins (H_2L_2) (see the gel in Figure 2b, track 4). 1981 Valle concludes that "the oocyte both assembles and secretes immunoglobulin" (page 339, column 2, ¶2, lines 1-7). Although Valle discloses with respect to Figure 2a (Track 3) that little secreted tetrameric immunoglobulin is found in the oocyte media, Valle explains that after secretion, the immunoglobulin is oxidized in the oocyte culture medium. (See Page 338, Col. 2) Therefore, Valle adds horse serum to the oocyte medium to prevent such oxidation after secretion (Figure 2b, Track 4 and explanation of Page 338, Col. 2). As shown in Figure 2b, Track 4, most of the secreted immunoglobulin is in a tetrameric form.

1981 Valle teaches modifying a cell with genetic material encoding the heavy chain and light chain of an immunoglobulin, followed by expressing both chains in a single cell, which chains assemble into an immunoglobulin that is secreted from the cell. Valle is pertinent to the dependent claims of Cabilly II that recite that the expressed immunoglobulin is secreted from the cell in which produced.

5. Dallas WO 82/03088

Dallas teaches that two different proteins (in addition to a selectable marker) can be expressed in a single cell and such expression may be accomplished by the use of two vectors, each containing DNA encoding one of the proteins, or by use of a single vector that contains DNA encoding each of the proteins. (See Example IV, as well as

page 8, lines 9-11, which disclose the use of a single vector, and page 9, lines 27-29, which discloses the use of two vectors).

Dallas teaches the production of a plasmid expressing two heterologous proteins. A *Hin*dIII fragment containing DNA encoding one of the proteins was removed from a plasmid and inserted into a second plasmid that included DNA encoding the second protein as a *BamHI* fragment (page 8, lines 11-17 and at page 7, lines 29-33). As a result, the two plasmids used for expressing the two proteins in a single cell were used to generate a single plasmid for expressing both proteins in a single cell. Because the DNA encoding each heterologous protein was inserted using a different restriction site (*Bam*HI and *Hin*dIII have no isoschizomers and each recognizes a unique restriction sequence), the DNAs were necessarily inserted into different insertion sites of the same plasmid or vector.

Dallas is pertinent to the claims of Cabilly II that are directed to the use of a single vector for expressing the heavy and light chains (for example, claims 3 and 15).

6. Kaplan – European Patent Application No. 0 044 722 (Published January 27, 1982).

Kaplan teaches methodology for producing an immunoglobulin by recombinant DNA technology. Briefly, Kaplan discloses production of an immunoglobulin by isolating mRNA from a hybridoma cell, selecting mRNA encoding heavy and light chains using specific probes that hybridize to this mRNA, preparing the corresponding cDNA using reverse transcriptase, inserting said cDNA into a suitable vector, such as the plasmid pBR322, and using this to transform bacterial and yeast cells. (Kaplan at pages 8-10).

Kaplan teaches that the antibody can be produced in insoluble form, solubilized and refolded into a functional molecule (p. 10, lines 27-32). Kaplan further discloses that an antibody may be attached to a label or drug (p. 8, lines 7-21).

Kaplan is pertinent to claims of Cabilly II directed to exogenous production of an immunoglobulin in a cell in an insoluble form (for example, claims 10, 26-28, 31 and 32), and claims directed to linking an immunoglobulin to a drug or label (for example, claims 34-36).

7. Axel - U.S. Patent 4,399,216.

Axel teaches transforming a eukaryotic cell with exogenous DNA (DNA I) and with DNA (DNA II) encoding a selectable phenotype (see Claim 1). In Claim 7, for example, Axel discloses that DNA I may code for an antibody (an antibody is an immunoglobulin).

Axel further teaches that the eukaryotic cell may be a mammalian cell (Claim 12).

Axel is pertinent to Cabilly II claims directed to the use of mammalian cells (for example, claims 19 and 20).

8. Rice, Regulated expression of an immunoglobulin gene introduced in a mouse lymphoid cell. Proc. Natl. Acad. Sci. 79, pages 7862-65 (Dec. 1982).

Rice discloses that a mammalian cell can be transformed with DNA to express an immunoglobulin light chain, and that the expressed exogenous light chain assembles with a heavy chain expressed in the cell to produce an immunoglobulin (see Abstract).

Rice is pertinent to claims of Cabilly II directed to the use of mammalian cells (for example, claims 19 and 20). The accompanying Declaration of Dr. Baltimore (Appendix D) explains the teachings of Rice in this respect.

9. Ochi, Nature, Vol. 302, pp. 340-342 (24 March 1983).

Ochi discloses the production of an exogenous light chain of an immunoglobulin specific for 2,4,6–trinitrophenyl (TNP) in a mammalian cell that produces an

endogenous heavy chain of such immunoglobulin (See Figures 1 & 2). Ochi demonstrated that such cells produced an immunoglobulin specific for TNP (see last full paragraph on Page 340, as well as Figure 2 and Table 1). Moreover, such immunoglobulin specific for TNP was secreted from the cells (See Table 1).

Thus, Ochi teaches that an exogenous immunoglobulin chain that is produced in a mammalian cell is capable of combining in a cell with the corresponding immunoglobulin chain produced in the cell to produce an immunoglobulin that is secreted from the cell and is specific for its corresponding antigen.

10. Oi, Proc. Natl Acad Sci USA, Vol. 80, pages 825-829 (February 1983).

Oi discloses the production of an assembled immunoglobulin by transforming a mammalian cell (a hybridoma) with a vector encoding an immunoglobulin light chain. The expressed light chain assembles with an endogenous immunoglobulin heavy chain to produce an assembled immunoglobulin that is secreted from the cell. Oi is relevant to the claims of Cabilly II that claim the use of a mammalian cell.

B. Disclosure of Cabilly II and Scope of Cabilly II Claims

In contrast to each of Deacon, 1981 Valle and 1982 Valle, the experiments performed by Cabilly II did not demonstrate that an immunoglobulin was produced in the cell in which heavy and/or light chain was expressed. In each of the experiments, Cabilly II expressed heavy and/or light chain in a cell and then produced an immunoglobulin outside of the cell by assembling expressed heavy and light chains outside the cell.

Moreover, the experiments of Cabilly II were performed with respect to only one immunoglobulin (CEA antibody) in one type of cell (E. coli) using one type of expression

technique (expression of the chains as insoluble bodies, lysing of the cells, solubilizing the chains, recovering the chains and assembling the chains in vitro).

Based on such experimental evidence, Cabilly II has claims that purport to cover (i) the use of any and all types of host cells and (ii) the use of expression techniques where the chains are assembled in the cell and secreted from the cell (for example, claim 9)[5] as well as expression techniques where the chains are assembled outside of the cell.

For example, Claims 1-5, 9-14, 17, 19, 20 and 33-36 are of a scope to cover the use of any mammalian host cell, including cells that are known to produce and secrete functional immunoglobulins, such as hybridomas. As a result, such claims of Cabilly II in fact cover the expression of two immunoglobulin chains that are known to assemble into a functional immunoglobulin by transforming a mammalian cell of a type that is known to express and assemble immunoglobulin chains in a single cell and is known to secrete such assembled chains as a functional immunoglobulin.

As hereinafter indicated, once it was known that each of an exogenous immunoglobulin heavy chain and exogenous immunoglobulin light chain could be expressed in a cell (the claims of Cabilly I), it would have been obvious to express such two chains in a single cell (and in particular, a mammalian cell known to have the capability to assemble and secrete functional immunoglobulins) in view of prior art such as Deacon or 1981 Valle or 1982 Valle or Ochi. Such an obvious modification of the claims of Cabilly I meets all of the limitations of such claims of Cabilly II.

Moreover, most of the claims are of a breadth to cover the production of an immunoglobulin that does not have binding affinity for an antigen. In this respect, note

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[5] The only reference in Cabilly II with respect to producing both heavy and light chains in a single host cell so that they might possibly be secreted from the cell as an immunoglobulin is found in Col. 12, lines 50-56; however, such disclosure is speculative and general without any specific details, and is limited to microbial host cells.

that Cabilly II discloses that an immunoglobulin encompasses those that have specificity for an antigen and those that do not have such specificity (for example, Col. 6, lines 3-11).

C. Application of Prior Art to Claims of Cabilly II

As set forth in detail below, the claims of Cabilly II are obvious variants of the claims of Cabilly I in light of the prior art cited herein.

1. Comparison of Claim 1 of Cabilly II to Claim 1 of Cabilly I

(a) Introductory Portion of Claim 1 of Cabilly II

Claim 1 of Cabilly II includes an introductory portion that recites that an immunoglobulin is produced in a single host cell.[6]

The claims of Cabilly I do not specifically disclose producing an immunoglobulin in a single cell.

(b) Part (i) of Claim 1 of Cabilly II

Claim 1 of Cabilly II claims transforming a single host cell with a first DNA sequence encoding at least the variable domain of an immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of an immunoglobulin light chain.

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[6] It is noted that claim 1 does not recite that the produced immunoglobulin is immunologically functional, whereby claim 1 is of a breadth to cover a process that produces a non-immunologically functional immunoglobulin. As a result, the Owners are not in a position to argue that an obvious variant of the claims of Cabilly I must produce a functional immunoglobulin. Nonetheless, Deacon and 1982 Valle provide experimental evidence that the assembled immunoglobulin is immunologically functional. Therefore, the obvious modification of the claims of Cabilly I would produce an immunologically functional immunoglobulin.

Claim 1 of Cabilly I discloses transforming a host cell with a DNA sequence encoding at least the variable domain of an immunoglobulin heavy chain wherein the heavy chain is chimeric. Such chimeric heavy chain of the claims of Cabilly I is an immunoglobulin chain that contains at least the variable domain.

Claim 1 of Cabilly I also discloses transforming a host cell with a DNA sequence encoding at least the variable domain of an immunoglobulin light chain wherein the light chain is chimeric. Such chimeric light chain of the claims of Cabilly I is an immunoglobulin chain that contains at least the variable domain.

Claim 1 of Cabilly I does not specifically disclose transforming a single host cell with each of such DNA sequences.

(c) Part (ii) of Claim 1 of Cabilly II

Claim 1 of Cabilly II claims independently expressing the two DNA sequences to produce the heavy and light chains as separate molecules in a single transformed host cell.[7]

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[7] Step (ii) of Claim 1 of Cabilly II, as well as independent process claim 33 recite that the heavy and light chains are produced as "separate molecules in said single host cell ... (emphasis added)", whereby consistent with the working examples of Cabilly II, the two chains while in the cell are separate molecules, which chains are assembled outside of the cell. The Owner may argue that the introductory portion of claims 1 and 33 recite that the immunoglobulin is produced in a single cell, whereby such claims are directed to assembly of the chains in the cell. However, such an argument is inconsistent with dependent claim 10, the working examples of Cabilly II, the Cabilly II disclosure, which only speculates as to the possibility of assembly in a microbial cell, and the written description requirements of 35 USC 112. In any event, Deacon, 1981 Valle and 1982 Valle disclose production of two exogenous immunoglobulin chains in a single cell and assembly of the chains in the single cell. In addition, each of Rice, Ochi and Oi teach that an exogenous immunoglobulin light chain produced in a cell assembles with an endogenous heavy chain produced in such cell, thereby teaching to one skilled in the art that exogenous immunoglobulin chains produced in a single cell will assemble in the cell.

Claim 1 of Cabilly I discloses inserting the heavy or light chain sequences into an expression vector operably linked to a suitable promoter, transforming the host cell with the vector, culturing the host cell, and recovering the chains from the culture. Thus, such process implicitly discloses independently expressing each of the DNA sequences encoding a chimeric heavy chain or chimeric light chain to produce a chimeric heavy chain or chimeric light chain as a separate molecule.

Claim 1 of Cabilly I does not specifically disclose producing such two chains in a single host cell.

2. Difference Between Claim 1 of Cabilly II and Claims of Cabilly I

Claim 1 of Cabilly II differs from the claims of Cabilly I by reciting that the "transforming" and "expressing" occurs in a single cell to produce "an immunoglobulin in a single host cell."

The present case is directly analogous to that in Eli Lilly v. Barr Laboratories, 251 F.3d 955, 58 U.S.P.Q.2d 1869 (Fed. Cir. 2001), in which a later patent was held to be invalid for obviousness-type double patenting over an earlier, co-owned patent relating to the drug fluoxetine for the treatment of anxiety. In particular, the Federal Circuit focused on whether two elements provided a distinction between the subject claims of each patent:

> The relevant portion of claim 1 of the '213 patent is directed to a method for treating anxiety in a human by administering an effective amount of fluoxetine or a pharmaceutically-acceptable salt thereof. '213 patent, col. 2, ll. 34-39. Claim 7 of the '549 patent covers a method of blocking the uptake of serotonin by brain neurons in animals by administering the compound fluoxetine hydrochloride. '549 patent, col. 20, ll. 7-9 (emphasis added) [58 U.S.P.Q. 2d at 1878]

Thus, the claim of the earlier patent specified the species method of treating anxiety and the genus compound fluoxetine or a salt. Conversely, the claim of the later patent specified the genus method of blocking serotonin uptake, and the species compound of the hydrochloride salt of fluoxetine. For the method, the Federal Circuit found that the species anticipated the genus, and that the genus of the later claim provided no patentable distinction; i.e., blocking serotonin uptake was not patentably distinct over the anticipatory treatment of anxiety. Consequently, double-patenting turned on whether the hydrochloride salt was obvious over the earlier claimed fluoxetine and salts thereof. The Federal Circuit held that the species (hydrochloride salt) was obvious and, therefore, the claim was invalid for obviousness-type double patenting.

Similarly, the Cabilly I claim specifies the species of chimeric immunoglobulin chains, and the genus of expressing a heavy chain or light chain. Cabilly II claims the genus of all immunoglobulin chains, and the species of expressing both a heavy chain and a light chain gene in a single cell to produce an immunoglobulin. As in Lilly, the Cabilly II genus of all immunoglobulin chains provides no patentable distinction over the Cabilly I species of chimeric immunoglobulin chains. Thus, as in Lilly, the question of double patenting turns on whether the species of expressing both chains in a single cell to produce an immunoglobulin of the Cabilly II claim is non-obvious over the earlier claimed genus—expressing a heavy chain or a light chain.

As set forth in detail below, expressing a heavy and a light chain in a single cell to produce an immunoglobulin is obvious over expressing and recovering a heavy chain or a light chain. First, the natural cellular production of immunoglobulins was well understood in the prior art to entail the expression of both chains. Second, expression of exogenous heavy and light chains in a single cell to produce an immunoglobulin had been demonstrated by the prior art, namely Deacon, 1981 Valle and 1982 Valle. Therefore, the Cabilly II claims are invalid for obviousness-type double patenting over the claims of Cabilly I.

Moreover, the recitation of "producing an immunoglobulin" in claim 1 of Cabilly II cannot be regarded as a patentable distinction by itself. In Geneva Pharmaceuticals v. GlaxoSmithKline, supra, the Federal Circuit held that a claim directed to an obvious utility of previously claimed subject matter does not warrant the granting of a second patent, absent a terminal disclaimer. In the present case, expressing each of the chains of Cabilly I in a single cell to produce an immunoglobulin is an obvious utility of the process claimed in Cabilly I. Therefore, this recitation provides no patentable distinction over the claims of Cabilly I. In any event, this utility is also clearly disclosed in the prior art, as set forth in detail below.

3. Claim 1 of Cabilly II is an Obvious Variant of the Claims of Cabilly I

A. Claims of Cabilly I in Combination with Deacon or 1981 Valle or 1982 Valle

Claim 1 of Cabilly II is an obvious variant of Claim 1 of Cabilly I in view of Deacon or 1981 Valle or 1982 Valle for the following reason:

(i) As previously indicated, Claim 1 of Cabilly I discloses "transforming" and "expressing" the immunoglobulin chains of Claim 1 of Cabilly II in that the specific chains of Claim 1 of Cabilly I (the chimeric chains) are a species of the immunoglobulin genus of Claim 1 of Cabilly II. Eli Lilly v. Barr Laboratories, supra.

(ii) Claim 1 of Cabilly II differs from the claims of Cabilly I by reciting that the heavy and light immunoglobulin chains are produced in a single cell to produce an immunoglobulin in a single cell.

(iii) Each of Deacon, 1981 Valle and 1982 Valle disclose producing an immunoglobulin in a single cell by expressing heavy and light immunoglobulin chains in a single cell, whereby the expression of the heavy and light chains of the claims of

Cabilly I in a single cell to produce an immunoglobulin is an obvious variant of the claims of Cabilly I.

More specifically, Deacon and 1982 Valle disclose that an immunoglobulin can be produced in a single cell that does not produce such an immunoglobulin by transforming the same host cell with an RNA sequence encoding an immunoglobulin heavy chain (an antibody heavy chain) and an RNA sequence encoding an immunoglobulin light chain (an antibody light chain) and expressing the heavy and light chains in the transformed host cell which assemble into a functional immunoglobulin (one that binds to the corresponding antigen).

Deacon and 1982 Valle, therefore, teach that a single cell can be modified to include genetic material encoding an immunoglobulin heavy chain and an immunoglobulin light chain and that the heavy and light chains expressed therefrom assemble into a functional immunoglobulin. Based on such teaching, it would have been obvious to one skilled in the art to perform the chimeric heavy chain production as claimed in Claim 1 of Cabilly I and the chimeric light chain production as claimed in Claim 1 of Cabilly I in a single cell to produce an immunoglobulin. Since the only difference between claim 1 of Cabilly II and the claims of Cabilly I is that the claims of Cabilly II are directed to performing in a single cell the steps disclosed by Cabilly I with respect to the heavy chimeric chain and with respect to the light chimeric chain to produce an immunoglobulin, Claim 1 of Cabilly I, as modified by Deacon or 1982 Valle, meets all of the limitations of Claim 1 of Cabilly II. Therefore, Claim 1 of Cabilly II is unpatentable based on obviousness-type double patenting.

The patentee may argue that Deacon, 1981 Valle and 1982 Valle used RNA to express the immunoglobulin chains, whereas Claim 1 of Cabilly I is directed to the use of DNA. Such an argument has no merit.

Each of Deacon, 1981 Valle and 1982 Valle is primarily relied on for its teaching that exogenous heavy and light chains that are produced in a single cell assemble into

an immunoglobulin. Since the claims of Cabilly I are drawn to exogenous production of an immunoglobulin heavy chain and also claim exogenous production of an immunoglobulin light chain, and each of Deacon, 1981 Valle and 1982 Valle teach one skilled in the art that when such two chains are exogenously produced in a single cell, such two chains assemble into an immunoglobulin, it would be obvious to modify the process of the Cabilly I claims to exogenously produce each of the heavy and light chains claimed by Cabilly I in a single cell in order to assemble such chains into an immunoglobulin. The teachings of each of Deacon, 1981 Valle and 1982 Valle that heavy and light chains exogenously produced in a single cell assemble into an immunoglobulin does not depend upon the genetic material used for such production, i.e., once expressed, the ability of the two chains to assemble into an immunoglobulin does not depend on the genetic material used for such expression.

Recombinant production of an exogenous protein necessarily involves transcription of the exogenous DNA to produce exogenous mRNA. The exogenous mRNA is then translated into exogenous protein.

Therefore, when the claims of Cabilly I are modified to express both chains in a single cell to produce an immunoglobulin as taught by each of Deacon, 1981 Valle and 1982 Valle, in the modified process of the claims of Cabilly I, as in each of Deacon, 1981 Valle and 1982 Valle, the exogenous heavy and light chains are expressed from exogenous mRNA.

When Claim 1 of Cabilly I is modified as suggested by Deacon or 1981 Valle or 1982 Valle, such modified Claim 1 of Cabilly I meets all of the limitations of Claim 1 of Cabilly II.

Moreover, in an opposition proceeding in Europe, one of the owners of Cabilly II (Genentech, Inc.) opposed a European patent granted to Celltech Limited (the "Boss Patent") that contained the following claim:

> A process for producing a heterologous Ig molecule or an immunologically functional Ig fragment in a single host cell, which comprises transforming the host cell with separate DNA sequences respectively encoding polypeptide chains comprising at least the variable domains of the Ig heavy and light chains and expressing each of said polypeptide chains separately in said transformed single host cell. [Appendix C, p. 1, A.1.1]

Such claim is essentially identical to claim 1 of Cabilly II. The opposition papers submitted by Genentech are attached as Appendix C.

In the Opposition, Genentech asserted that the Boss claims were not patentable over 1982 Valle. In particular, Genentech asserted that such reference disclosed synthesis of the immunoglobulin in a cell by microinjecting a single cell with mRNA encoding the heavy and light chain of the immunoglobulin and that such reference demonstrated that the immunoglobulin that was produced in the cell was immunologically functional, and that the method disclosed was indistinguishable from that claimed by Boss.

Indeed, Genentech argued that the Boss claims were anticipated by (lacked novelty) or at least were obvious (lacked inventive step) over 1982 Valle. Specifically, Genentech stated:

> 2.3 Accordingly, Document 2 (Valle) clearly teaches the production of an immunologically functional heterologous immunoglobulin molecule in eukaryotic cell transfected by separate DNA molecules encoding its heavy and light chains, respectively. In view of the broad implications evidenced by the Abstract, the fact that the actual experiment was performed with microinjected mRNAs is not relevant. In any event, because the messenger RNA carries the information from DNA to the ribosomal sites of protein synthesis, it is functionally equivalent to DNA.
> (Emphasis added.) [Appendix C, p. 17, C. 2.3]

Although such admission by Genentech is not required to establish that the claims of Cabilly II are an obvious variant of the claims of Cabilly I, based on the teachings in the art (Deacon, 1981 Valle or 1982 Valle) such admission by the patentee is consistent with the unpatentability of the claims of Cabilly II based on obviousness-type double patenting.

The patentee may argue that Claim 1 of Cabilly I only discloses independent expression of the chimeric light chain in one cell and the independent expression of the chimeric heavy chain in another cell.

Even if the disclosure of Claim 1 of Cabilly I is construed to be limited to independent expression of the two chimeric chains in two different cells (it is not), since Claim 1 of Cabilly II also claims "independently expressing" the two chains, the difference between such purportedly limited disclosure of Claim 1 of Cabilly I and Claim 1 of Cabilly II is that Claim 1 of Cabilly II defines that the independent expression is performed in a single cell, rather than two cells.

The performance of independent expression of heavy and light chains in a single cell as claimed in Cabilly II is an obvious variant of independent expression in two cells in that in each of such cases, the expression of the heavy chain and of the light chain function independently of each other. Since Deacon, 1981 Valle and 1982 Valle disclose that it is known in the art to modify a single cell to express both the heavy and light chain of an immunoglobulin in a single cell to produce an assembled immunoglobulin, Claim 1 of Cabilly II, even though limited to expressing both chains in a single cell, is an obvious variant of Claim 1 of Cabilly I.

The decision of In re Ockert 245 F2d 467, 114 USPQ 330 (CCPA 1957) is of relevance on this point even though the decision does not involve biotechnology in that Ockert recognized that where a claim of a patent claims the performance of two independent steps in different vessels, claims of an application that claim the

performance of such two steps in a single vessel are not patentable, based on obviousness-type double patenting.

In re Ockert involved appeals from a Board decision affirming double patenting rejections of pending applications over a patent to Ockert. The Ockert patent claimed a continuous process for separating organic compounds using an adsorbent and involved passing the sample through an adsorbing column and then to a second column for desorption, thus defining adsorption and desorption zones in separate columns. One of the applications on appeal contained a claim to carrying out both adsorption and desorption in the same column, with the adsorption zone near the top and the desorption zone near the bottom of the same column. In affirming the rejection, the court observed,

> We are of the opinion that the determination as to whether one or two columns are to be used involves merely a matter of choice or design and that it would be obvious to a skilled worker to use one column or two as might be dictated by considerations of convenience or expediency. The adsorption and desorption zones function in the same way, whether or not they are located in a single column. [114 USPQ at 332-333]

Similarly, Claim 1 of Cabilly II claims the same steps claimed in Claim I of Cabilly I (transforming a host cell with DNA encoding a heavy chain or a light chain and independent expression to produce such heavy or light chain); however, unlike Claim 1 of Cabilly I, Claim 1 of Cabilly II is limited to performing such steps in a single cell. As in Ockert, the transformation of a cell with heavy chain or light chain as claimed in Claim 1 of Cabilly I is not changed when performed in a single cell as compared to two different cells, and the independent expression of heavy chain and light chain does not change when performed in a single cell instead of two different cells. As a result, performing the steps disclosed in Claim 1 of Cabilly I in a single cell is an obvious variant of Claim 1 of Cabilly I, in view of Deacon or 1982 Valle each of which discloses that a single cell can be modified to express the heavy and light chain of an immunoglobulin to produce a functional immunoglobulin.

The position herein taken is further supported by Geneva Pharmaceuticals v. GlaxoSmithKline, supra.

In the Geneva case, the court considered the issue of obviousness-type double patenting and determined that a method of inhibiting β-lactamase in an animal arising from β-lactamase producing bacteria by administration of a β-lactamase inhibiting amount of clavulanic acid or pharmaceutically acceptable salt thereof was invalid over a product claim of the Fleming Patent, which claimed potassium clavulanate. The claims in issue were as follows:

Fleming (U.S. 4,367,175)	'720 Patent
1. Potassium clavulanate of the formula _____ having a molar extinction coefficient as determined in 0.1M aqueous potassium hydroxide using ultraviolet light of wavelength 258 nm of about 17000.	1. A method of effecting β-lactamase inhibition in a human or animal in need thereof arising from a β-lactamase producing bacteria which comprises administering to said human or animal a β-lactamase inhibitory amount of clavulanic acid or a pharmaceutically acceptable salt thereof.

The court held that it could consider the specification of the Fleming Patent and the specification of the patent that contained the claim in issue in order to ascertain any overlap in claim scope for the double-patenting comparison.

The court determined that the Fleming Patent disclosed a use of potassium clavulanate for combating bacteria that produce β-lactamase and, therefore, the patent in issue claims nothing more than the Fleming Patent's disclosed utility for the claimed compound in terms of a method of use, stating:

> The '720 patent claims nothing more than Fleming's disclosed utility as a method of using the Fleming compound. Thus, the claims of the Fleming and '720 patents are not patentably distinct. This court affirms the district court's judgment that the '720 patent is invalid for nonstatutory double patenting over the Fleming patent. [349 F.3d at 1386, 68 U.S.P.Q. at 1875.]

In examining Cabilly I and Cabilly II (the disclosures are identical), the only claimed use for producing each of the heavy chimeric chain and the light chimeric chain as claimed in claim 1 of Cabilly I is for assembling the two chains into an immunoglobulin (for example, see the Summary of the Invention of Cabilly I, col. 4, line 55 – col. 5, line 46).

As in the Geneva case, to the extent that the claims of Cabilly II are directed to producing a heavy chain and a light chain that are assembled into an immunoglobulin, such claims of Cabilly II are directed to nothing more than the utility disclosed in Cabilly I for producing each of the heavy and light chains as claimed in Cabilly I. Accordingly, as in the Geneva case, the claims of Cabilly II by reciting the production of an immunoglobulin are not patentably distinct from the claims of Cabilly I in that such recitation is nothing more than the utility for the expressed two chains disclosed in Cabilly I.[8]

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[8] Although the Owners Response (Pages 17-20) provide reasons as to why it may be desirable to express the heavy and light chains in different cells, there are also obvious reasons for expressing both chains in a single cell (such chains assemble into an immunoglobulin as disclosed by Deacon, 1981 Valle and 1982 Valle). The fact that each alternative may have certain advantages does not indicate that one is not an obvious modification of the other. Moreover, the assertion that there may be other utilities for the claimed method does not change the fact that Cabilly II is merely claiming a clearly obvious utility of the Cabilly I claimed method.

Even if the Geneva case is not considered to be applicable to the present case (it is applicable), claim 1 of Cabilly II is an obvious variant of the claims of Cabilly I based on Deacon, 1981 Valle or 1982 Valle.

The claims of Cabilly I provide the teaching that exogenous DNA encoding an immunoglobulin light chain can be expressed in a cell and that such expression produces the immunoglobulin light chain. Similarly Cabilly I provides the teaching that exogenous DNA encoding an immunoglobulin heavy chain can be expressed in a cell and that such expression produces the immunoglobulin heavy chain.

As a result, exogenous production of each of an immunoglobulin light chain and an immunoglobulin heavy chain by use of DNA encoding such chain is taught by the claims of Cabilly I. Based on Deacon, 1981 Valle and 1982 Valle, one skilled in the art would understand that for at least three different immunoglobulins, the art had demonstrated that exogenous light and heavy chains when produced in a single cell assemble into an immunoglobulin.

Once it was known from any of Deacon and/or 1981 Valle and/or 1982 Valle that when exogenous heavy and light chains are produced in a single cell, such chains assemble into an immunoglobulin, it would have been obvious to express the heavy and light chains of the claims of Cabilly I in a single cell in order to assemble the two chains into an immunoglobulin as taught by any of Deacon, 1981 Valle or 1982 Valle.

B. Claims of Cabilly I in Combination with Ochi

As an additional and independent ground for reexamination, Claim 1 of Cabilly II is unpatentable based on obviousness-type of double patenting when the claims of

Cabilly I are considered in combination with the teachings of Ochi.[9]

Based on the teachings of Ochi that an exogenous light chain of an immunoglobulin that is produced in the same cell as an endogenous heavy chain of such immunoglobulin produces an immunoglobulin that is immunologically functional, one skilled in the art would have found it to be obvious to express the light chain of the claim of Cabilly I and the heavy chain of the claims of Cabilly I in a single cell to produce a functional immunoglobulin.

The claims of Cabilly I teach the production in a cell of each of an exogenous light chain and an exogenous heavy chain. Once it was know that exogenous immunoglobulin chains could be produced in a cell (the Claims of Cabilly I) and that an exogenous immunoglobulin chain produced in a cell was capable of combining with its corresponding immunoglobulin chain to produce a functional immunoglobulin (Ochi), one skilled in the art would have been taught to express both chains of the claims of Cabilly I in a single cell to produce a functional immunoglobulin. As a result, Claim 1 of Cabilly II is unpatentable based on obviousness type double patenting, when the claims of Cabilly I are considered in combination with Ochi.

4. Claims Dependent on Claim 1

As hereinafter indicated, Claims 2-14, 19, 34 and 35 which are dependent on Claim 1 are directed to the use of conventional recombinant techniques with respect to the subject matter claimed in Claim 1 of Cabilly II. Therefore, such dependent claims do not add any patentably distinguishable subject matter and are also obvious variants of the claims of Cabilly I.

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[9] The combination of Cabilly I with 1981 Valle or 1982 Valle or Deacon is not dependent on the teachings of Ochi and, therefore, the claims of Cabilly I in combination with Ochi provides an independent basis for finding Claim 1 of Cabilly II to be unpatentable based on obviousness-type double patenting.

Claims 2 and 3 of Cabilly II define that the DNA sequences used for expressing the heavy chain and light chain are present in either different vectors or the same vector. Since Claim 1 of Cabilly I discloses the use of two vectors (one for the light chain and one for the heavy chain), claim 2 is an obvious variant of Claim 1 of Cabilly I in view of Deacon, 1981 Valle, 1982 Valle or Ochi as applied above with respect to Claim 1 of Cabilly II.

Claim 3 of Cabilly II recites that the two DNA sequences are in a single vector. Dallas discloses that when it is desirable to produce two proteins in a single cell, the two proteins may be produced by use of two vectors (plasmids), each of which expresses DNA encoding one of the two proteins, or by use of a single vector (plasmid) that contains DNA encoding each of the two proteins. Since Dallas discloses that the use of a single vector for expressing two proteins and use of two vectors for expressing two proteins are well known alternatives, Claim 3 of Cabilly II is an obvious variant of Claim 1 of Cabilly I in view of Deacon, 1981 Valle, 1982 Valle or Ochi.

Claim 4 of Cabilly II depends on claim 3 and defines a plasmid as the single vector. Dallas discloses a plasmid (see, for example, page 3, lines 33-35). Ochi discloses a plasmid for expressing an exogenous immunoglobulin chain (See Figure 1). Claim 4 is therefore an obvious variant of Claim 1 of Cabilly I in view of Deacon, 1981 Valle, 1982 Valle or Ochi.

Claim 5 of Cabilly II depends on claim 4 and limits the plasmid to pBR322. Dallas also discloses use of the plasmid pBR322 (see page 6, line 1), whereby Claim 5 is an obvious variant of Claim 1 of Cabilly I.

Claims 6-8 of Cabilly II are drawn to the use of yeast or bacterial cells as the single host cell. The use of such cells was well known in the art and fails to render claims 6-8 patentable over claim 1 of Cabilly I, as modified by Deacon, 1981 Valle or 1982 Valle. Dallas teaches the use of E. coli cells (which are bacteria) for the

expression of multiple heterologous proteins. Thus, claims 6-8 claim are an obvious variant of claim 1 of Cabilly I in view of Deacon.

Claim 9 recites that the heavy and light chains are expressed and secreted from the cell as an immunologically functional immunoglobulin.

1981 Valle discloses exogenous production of the heavy and light chain of an immunoglobulin in a single cell, assembly in the cell and secretion of the assembled immunoglobulin from the cell. 1981 Valle did not test the secreted immunoglobulin to demonstrate that the immunoglobulin when secreted retains immunoglobulin binding ability; however, 1981 Valle concludes (Page 339, second column, in the paragraph bridging Pages 339 and 340) that it is likely that the secreted immunoglobulin retains specificity for its antigen (referring to the prior work of Deacon). Based on the teaching of 1981 Valle that exogenous production of heavy and light chains in a single cell produces an assembled immunoglobulin that is secreted from the cell and the suggestion that such a secreted immunoglobulin is functional, it would have been obvious to express the two immunoglobulin chains of claim 1 of Cabilly I to produce an assembled immunoglobulin that is secreted from the cell as a functional immunoglobulin, particularly where 1981 Valle discloses that no special steps are required to assemble and secrete such an immunoglobulin.

The owners may argue that 1981 Valle does not teach modification of the claims of Cabilly I as set forth above in the absence of direct data in 1981 Valle that the secreted immunoglobulin is functional. This argument has no merit. In addition, such an argument should not be considered in that Cabilly II also does not disclose such data.[10]

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[10] Cabilly only speculates (Col. 12, Lines 52-55) that it may be possible to secrete immunoglobulin produced in a microbial cell. All of the experiments only disclose expression in a cell, followed by lysing of the cell and in vitro assembly of the chains. There is no data in Cabilly II which purports to demonstrate that exogenous chains produced in the cell assemble in the cell to produce immunoglobulin that is secreted as functional immunoglobulin.

Since 1981 Valle contains more information and data than Cabilly II with respect to assembly of expressed immunoglobulin in a cell and secretion thereof from the cell, in good faith, the owners can not argue that 1981 Valle does not teach one skilled in the art to modify the claims of Cabilly I to express both chains in a single cell to produce immunoglobulin that is secreted from the cell as a functional immunoglobulin, without also admitting that Cabilly II lacks such a teaching, thereby rendering claim 9 invalid under 35 USC 112.

In addition, Ochi teaches that an exogenous immunoglobulin light chain that is produced in the same cell as an immunoglobulin heavy chain assembles into an immunoglobulin that is secreted from the cell as a functional immunoglobulin. As a result of such teachings, one skilled in the art would have found it to be obvious to produce the two chains of Claim 1 of Cabilly I in a single cell to produce a functional immunoglobulin that is secreted from the cell. As a result, Claim 9 is unpatentable based on obviousness-type double patenting based on a combination of the claims of Cabilly I and Ochi.

Claim 10 of Cabilly II recites that the heavy and light chains are produced in insoluble form, and are solubilized and refolded into a functional molecule. Kaplan discloses that such a technique is applicable to the production of recombinant immunoglobulin. (See Kaplan Page 10, Lines 27-32) As a result, the use of the technique claimed in Claim 10 is an obvious variant of Claim 1 of Cabilly I when expressing both immunoglobulin chains in a single cell.

Claim 11 of Cabilly II depends from claim 1 and recites production of a complete immunoglobulin. Each of 1982 Valle and Deacon discloses producing functional immunoglobulin of defined specificity when both heavy and light chains are expressed in a single cell. As a result, Claim 11 is an obvious variant of the claims of Cabilly I in view of Deacon or 1982 Valle.

Claim 12 of Cabilly II depends from claim 1 and recites that the constant and variable regions are derived from the same source. Each of 1981 Valle, 1982 Valle and Deacon teaches production of heavy and light chains where the constant and variable regions are derived from the same source (the spleens of a group of immunized rats). As a result, Claim 12 is an obvious variant of the claims of Cabilly I in view of Deacon, 1981 Valle or 1982 Valle.

Claim 13 of Cabilly II depends from claim 1 and recites DNAs encoding chains wherein the constant domain is from a different species or class than the variable domain (i.e., chimeric chains, as disclosed in claim 1 of Cabilly I). Since Claim 1 of Cabilly I discloses the production of such chains, Claim 13 is an obvious variant of Claim 1 of Cabilly I in view of Deacon, 1981 Valle or 1982 Valle.

Claim 14 of Cabilly II depends from claim 1 and defines that the two DNA sequences are derived from a hybridoma. Hybridomas are well known sources of DNA encoding the heavy and light chains of an immunoglobulin. For example, each of 1981 Valle and Kaplan teach that the genetic material used for expressing both a heavy and light chain may be obtained from a hybridoma. As a result, Claim 14 is an obvious variant of the claims of Cabilly I in view of Deacon, 1981 Valle or 1982 Valle.

With regard to Claim 19 of Cabilly II which recites that the host cell is a mammalian cell, it was well known in the art to use mammalian cells for recombinant protein production; for example Axel (Col. 5, lines 3-7 and 24-28 and claims 19 and 20), Rice (P 7863), Ochi and Oi, each of which discloses the use of mammalian host cells for recombinant protein production and each refer to immunoglobulin production in such cells.[11] In this respect, also note the Declaration of Dr. Baltimore as to the applicability of Rice to the Cabilly II claims. As a result, the use of mammalian host cells is an

[11] It is again noted that Axel discloses (i) that DNA I produces an antibody (claim 7) whereby DNA I necessarily produces two chains and (ii) that DNA I may be more than one gene (see Abstract).

obvious variant of Claim 1 of Cabilly I when expressing both immunoglobulin chains in the same host cell.

With regard to Claims 34 and 35 of Cabilly II, such claims recite the step of attaching the immunoglobulin to a label or drug. The attachment of an immunoglobulin to a label or drug was well known in the art; e.g., see Kaplan, P. 8, lines 7-21. As a result, the attachment defined in claims 34 and 35 is an obvious variant of Claim 1 of Cabilly I when expressing both chains in a single cell.

5. Independent Claim 15 of Cabilly II and the Claims Dependent Thereon

Claim 15 of Cabilly II claims a vector that includes a first DNA sequence encoding at least the variable domain of an immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of an immunoglobulin light chain, each located at different insertion sites.

The claims of Cabilly I (Claims 1 and 5) disclose a vector that includes the claimed first DNA sequence and a vector that includes the claimed second DNA sequence.

Claim 15 of Cabilly II differs from the claims of Cabilly I in that the claims of Cabilly I do not require that both DNA sequences are present at different insertion sites in the same vector.

Dallas discloses the use of two vectors, (two plasmids) each containing a DNA sequence encoding one of two proteins to be expressed in a single cell, or a single vector (single plasmid) that contains such two DNA sequences. (*See* Example IV of Dallas and discussion of Dallas in Section III. A.5 above.) In the single vector, the DNA is inserted at different insertion sites (two different restriction sites).

Based on the teachings of Dallas that two vectors, each containing a different DNA sequence expressing different proteins in a single cell, and a single vector

containing such two DNA sequences, are known alternatives to each other, combining the two vectors disclosed by Claims 1 and 5 of Cabilly I into a single vector by insertion of the two DNA sequences at different restriction sites is an obvious variant of Claims 1 and 5 of Cabilly I (just as taught by Dallas). As previously noted, any of Deacon, 1981 Valle or 1982 Valle teach one skilled in the art to exogenously produce both chains in a single cell.

Since Claim 15 differs from the claims of Cabilly I only with respect to the two DNA sequences being combined into a single vector, the teachings of Claims 1 and 5 of Cabilly I, as modified by Dallas, meet all the limitations of Claim 15 of Cabilly II.

Claim 16 of Cabilly II depends from claim 15 and limits the vector to a plasmid, the same kind of vector disclosed by Dallas (see above), whereby Claim 16 is an obvious variant of Claim 5 of Cabilly I in view of Dallas.

Claim 17 of Cabilly II is drawn to a host cell transformed with the vector of claim 15. The claims of Cabilly I and Dallas each disclose transforming a host cell. For the above-recited reasons, claim 17 is an obvious variant of the claims of Cabilly I in view of Dallas.

6. Claim 18 of Cabilly II and the Claims Dependent Thereon

Claim 18 of Cabilly II is directed to a transformed host that includes a vector containing DNA encoding at least the variable domain of an immunoglobulin heavy chain and a vector containing DNA encoding at least the variable domain of an immunoglobulin light chain.

Claim 18 of Cabilly II is an obvious variant of the claims of Cabilly I in view of Deacon, 1981 Valle, 1982 Valle or Ochi as set forth with respect to Claim 1 of Cabilly II. The obvious variant of the process of Claim 1 of Cabilly I in view of Deacon, 1981 Valle,

1982 Valle or Ochi includes a transformed host cell that includes the two vectors of Claim 18 of Cabilly II.

Claim 20 of Cabilly II recites that the transformed cell is a mammalian cell. The use of mammalian cells for immunoglobulin expression was known in the art (See discussion above with respect to Claim 19). When expressing both chains of Cabilly I in a single cell, the use of mammalian cells as defined in Claim 19 is an obvious variant of the claims of Cabilly I based on the general knowledge in the art, as exemplified by Axel or Rice or Ochi or Oi.

7. Claim 21 of Cabilly II and the Claims Dependent Thereon

Claim 21 of Cabilly II claims the production of an immunoglobulin that binds to a known antigen by preparing a vector containing DNA encoding an immunoglobulin light chain and heavy chain, which immunoglobulin has specificity for a particular, known antigen, transforming a eukaryotic or prokaryotic microbial host with the vector, culturing the host cell and recovering the immunoglobulin.

The claims of Cabilly I, as modified by Deacon, 1981 Valle, 1982 Valle or Ochi in the manner set forth above with respect to Claim 1 of Cabilly II, meet all of the limitations of Claim 21, except that the claims of Cabilly I do not specifically state that the DNA encoding the heavy and light chain are present in a single vector or that the host cell is a microbial host cell.

Claim 21 of Cabilly II, insofar as such claim is limited to the use of a single vector and the use of a microbial host cell, defines techniques of recombinant expression, that were well known prior to the effective filing date of Cabilly II. For example, Dallas discloses the use of a single vector and the use of microbial host cells (*See* Example 4). As a result, Claim 21 is an obvious variant of the claims of Cabilly I when considered with reference to Deacon, 1981 Valle, 1982 Valle or Ochi and that which was generally known in the art, as exemplified by Dallas.

With regard to claim 22, CEA is a known antigen and production of an immunoglobulin against such antigen by use of the modified process of claim 1 of Cabilly I is an obvious modification.

Claims 23 and 24 are directed to known immunoglobulin chains. The expression of an immunoglobulin with such a chain by the modified process of claim 1 of Cabilly I would have been obvious to one skilled in the art.

With regard to claim 25, the claims of Cabilly I are directed to a heavy chain and a light chain.

With regard to claims 26-28, 31 and 32 such features are well known expression procedures (see Kaplan above) and it would have been obvious to use such a procedure for expressing immunoglobulin chains in a single cell in the modified procedure of the claims of Cabilly I.

With regard to claims 29 and 30, see the above discussion with respect to claim 9 of Cabilly II.

8. Claim 33 of Cabilly II and the Claims Dependent Thereon

Claim 33 of Cabilly II is Claim 1 of Cabilly II, absent the transforming step of Claim 1 of Cabilly II.

The omission of the transforming step provides no patentable distinction over Claim 1. Thus, Claim 33 is an obvious variant of the claims of Cabilly I for the reasons hereinabove noted with respect to Claim 1 of Cabilly II.

As a result, Claim 33 of Cabilly II is unpatentable for obviousness-type double patenting based on the claims of Cabilly I in view of Deacon, 1981 Valle, 1982 Valle or Ochi.

Claim 36 of Cabilly II depends on Claim 33 and recites attaching the immunoglobulin to a label or drug. Such attachment was well known in the art (See above discussion with respect to Claims 34 and 35). Claim 36 is an obvious variant of the claims of Cabilly I when expressing both chains of Cabilly I in a single cell.

D. Rejection Of The Claims Of Cabilly II Is In Accordance With The Policy of Obviousness-Type Double Patenting

The judicially created doctrine of obviousness-type double patenting was created in order to protect the public against claims of the type issued in Cabilly II.

The claims of Cabilly I, although directed to production of a chimeric light chain or a chimeric heavy chain cover the production of both chains in a single cell in that production of both chains in a single cell necessarily includes the production of each of the chains.

One skilled in the art in reading the claims of Cabilly I would have understood that each of the heavy and light chains as claimed by Cabilly I is being produced for the purpose of assembling the two chains into an immunoglobulin.

Since Deacon and 1982 Valle each disclose that when a cell is genetically modified to produce two immunoglobulin chains in a single cell, such immunoglobulin chains assemble into a functional immunoglobulin, one skilled in the art would have immediately recognized that each of the two chains disclosed in the claims of Cabilly I should have been produced in a single cell (an embodiment covered by the claims of Cabilly I) in order to produce an immunoglobulin comprised of the two chains.

Upon expiration of Cabilly I, the public is entitled to practice obvious embodiments covered by the claims of Cabilly I. In light of the teachings of Deacon or 1981 Valle or 1982 Valle that a cell can be genetically modified to express two immunoglobulin chains in a single cell that assemble into an immunoglobulin, there is no embodiment of the claims of Cabilly I that is more obvious than producing each of the chains claimed by Cabilly I in a single cell to produce an immunoglobulin. The obviousness of such an embodiment is reinforced by the fact that the conventional technique for producing immunoglobulins involves the production of a modified cell (a hybridoma) in which both immunoglobulin chains are expressed in the same modified cell to produce a functional immunoglobulin.

Without a terminal disclaimer in Cabilly II (there is none), the public will not be able to practice such obvious embodiment covered by the claims of Cabilly I upon expiration of Cabilly I, whereby the claims of Cabilly II are not patentable based on obviousness-type double patenting.

V. CONCLUSION

The claims of U.S. Patent No. 6,331,415 (Cabilly II) are invalid for obviousness-type double patenting over claims 1-7 of U.S. Patent No. 4,818,567 (Cabilly I), in view of cited prior art that was not considered in the Pending Reexamination and did not form the basis for rejection of the claims therein. This represents a substantial new question of patentability and Cabilly II should be re-examined and found to be unpatentable based on obviousness-type double-patenting.

No additional fee is believed due in filing this request. If any fee is due, the Commissioner is requested to charge such fees, or credit any refunds, to Deposit Acc't No. 03-0678.

CERTIFICATE OF SERVICE

I hereby certify that on 12/23/05, a copy of the foregoing Request for Reexamination Under 35 U.S.C. § 302 and 37 C.F.R. § 1.510, including exhibits, was served upon the following via Federal Express:

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EXPRESS MAIL CERTIFICATE

Express Mail Label No. EV439773130US

Deposit Date: 23 DECEMBER 2005

I hereby certify that this paper and the attachments hereto are being deposited today with the U.S. Postal Service "Express Mail Post Office To Addressee" service under 37 CFR 1.10 on the date indicated above addressed to:

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