Commissioner’s Decision # 1269

Décision du Commissaire # 1269

TOPIC: B20, B22, C00

SUJET: B20, B22, C00

Application No.: 610,944

Demand no: 610,944

COMMISSIONER'S DECISION SUMMARY

C.D. 1269 Application No. 610,944

Excessive Width, Claims Broader in Scope than Teaching of Description (B20, B22, C00)

The application related to human-human hybridomas, monoclonal antibodies produced by the hybridomas, uses of the monoclonal antibodies and compositions comprising such antibodies. The examiner rejected the application saying that two claims were broader in scope than the teachings of the description and that they should be restricted to a particular monoclonal antibody. The Board disagreed and found that the description provided adequate support for a variety of monoclonal antibodies.

The application was returned to the examiner for further prosecution.

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 610, 944 having been rejected under Subsection 30(4) of the Patent Rules, the Applicant asked that the Final Action of the Examiner be reviewed. The rejection has been considered by the Patent Appeal Board and by the Commissioner of Patents. The findings of the Board and the decision of the Commissioner are as follows:

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This decision deals with a request that the Commissioner of Patents review the Examiner's Final Action on patent application number 610,944, filed on September 11, 1989 and entitled "METHOD OF PRODUCING HUMAN-HUMAN HYBRIDOMAS, THE PRODUCTION OF MONOCLONAL AND POLYCLONAL ANTIBODIES THEREFROM, AND THERAPEUTIC USE THEREOF". The Applicant is Kenneth Alonso, who is also the inventor.

A hearing before the Patent Appeal Board was held on May 7, 2003. Appearing on behalf of the Applicant was Mr. John Woodley and Mr. Michael Calucci from the firm of Sim & McBurney. The Patent Office was represented by Dr. Linda Brewer, the Examiner in charge of the application.

The application relates to a method of producing human-human hybridomas, to hybridomas produced by the method, to the production of monoclonal antibodies from the hybridomas, and to the use of monoclonal antibodies in the treatment of human disorders. In particular, the human-human hybridomas are produced by a method which involves sensitizing human spleen cells by mixing with human tumour cells in the presence of a spleen cell stimulating agent. The sensitized spleen cells are then fused with human B-lymphocytes and a hybridoma that produces monoclonal antibodies reactive with a specific human tumour antigen is selected.

There are 11 claims in the application. Claim 1 is directed to a method for producing human-human hybridomas. Claims 2 to 8 depend directly or indirectly on claim 1. Claim 9 is an independent claim directed to a method for making a cell line that produces monoclonal antibodies. Claim 10 is directed to the use of a monoclonal antibody produced by the method of claim 8 while claim 11 is directed to a composition containing this antibody.

The Examiner issued a Final Action on June 7, 2002 in which claims 10 and 11 were rejected under Subsection 174(2) of the Patent Rules as being broader in scope than the teaching of the description and thus not fully supported by the description. Claims 1 to 9 were identified in the Final Action as being allowable.

Claims 1 and 7 to 9, representative of the allowable claims, are as follows:

> 1. A method for the production of human-human hybridomas comprising the steps of:
> (a) providing a suspension comprising cells from a human tumour and a suspension comprising human spleen cells;
> (b) sensitizing the human spleen cells in suspension by mixing the cells with human tumour cells in the presence of a spleen cell stimulating agent;
> (c) fusing the human spleen cells and the human tumour cells with B-lymphocytes from a cell line distinct from the previously sensitized spleen cells;
> (d) screening the resultant fused cells to select at least one hybridoma that produces antibodies reactive with a specific human tumour antigen; and
> (e) cloning the selected hybridoma.
>
> 7. The method of claim 1 wherein the human tumour cells are colon adenocarcinoma cells, lung adenocarcinoma cells, breast adenocarcinoma cells, mucoepidermoic carcinoma cells, hepatocellular carcinoma cells, leiomyosarcoma cells, melanoma cells, neurofibrosarcoma cells, tongue

squamous carcinoma cells, pancreas adenocarcinoma cells, lymphoblast (acute leukemia) cells, Mycosis Fungoides cells, oat cell carcinoma cells, prostate adenocarcinoma cells, esophageal squamous carcinoma cells, Ewing's cells, gastric adenocarcinoma cells, biliary adenocarcinoma cells, ovary adenocarcinoma (mucinous) cells, ovary adenocarcinoma (serous) cells, lymphoblast (lymphoma) cells, alveolar cell carcinoma cells, squamous carcinoma cells of the anus, or glioblastoma cells.

8. A method of producing monoclonal antibodies to each of the carcinoma cells according to claim 7, which comprises culturing a hybridoma produced according to claim 7 in a culture medium and recovering said antibodies from said medium.

9. A method for producing a continuous cell line that produces monoclonal antibodies to a specific cancer comprising the steps of:

(a) sensitizing human spleen cells in suspension by mixing the cells with a spleen cell stimulating agent in the presence of human tumour cells;

(b) fusing the human spleen cells and the human tumour cells with human fetal marrow or lymphoblast cells to produce hybridomas ;

(c) selecting from among said hybridomas a hybridoma that produces antibodies reactive with only one human tumour antigen; and

(e) clonally expanding said selected hybridoma into a cell line.

Rejected claims 10 and 11 are as follows:

10. Use of a monoclonal antibody produced according to claim 8 for preparing a medicament for treating cancer.

11. A composition useful for treating cancer comprising a monoclonal antibody produced according to claim 8 and a pharmaceutically acceptable carrier.

In the Final Action, the Examiner stated, in part:

Claims 10 and 11 are broader in scope than the teaching of the description, thus are not fully supported by the description and fail to comply with Subsection 174(2) of the Patent Rules. Claim 10 is directed to the use of an allegedly novel product, a monoclonal antibody made by the method of claim 8, to to prepare a medicament. Claim 11 is directed to a composition comprising an allegedly novel product as principle ingredient, a monoclonal antibody made by the method of claim 8. The method of claim 8 is directed to producing many monoclonal antibodies by culturing hybridomas made using tumour cells named in claim 7, said hybridomas being made using the method of claim 1. Said hybridomas made using the named tumour cells and the monoclonal antibodies produced by said hybridomas are not fully disclosed in the description. Therefore, claim 10 encompasses the use of undisclosed monoclonal antibodies to prepare a medicament, and claim 11 encompasses compositions comprising undisclosed monoclonal antibodies. To comply with Subsection 174(2) of the Patent Rules claims 10 and 11 must specify that the "monoclonal antibody" used is the only monoclonal antibody specifically disclosed in the description, which is antibody NFS-84B to neurofibrosarcoma, deposited as ATCC Number HB983, as disclosed on page 30 (Example 2).

A Decision of the Commissioner of Patents concerning Canadian Patent 1,338,323 (issued May 14, 1996), published in the Canadian Patent Reporter, Feb. 4, 1998, Vol 76 (3d), pages 206-218, determined that exemplary support was required for claims to hybridoma cell lines and monoclonal antibodies as novel products. Without specific description, claims to these products were not considered to be allowable. While claims 10 and 11 are not directed to monoclonal antibodies as products, these claims are directed to a use and composition which rely on the novelty of specific monoclonal antibodies to impart novelty and utility to the claimed use and composition. The use and composition of claims 10 and 11 cannot be determined without specific monoclonal antibodies being identified for said use and in said composition.

.....

While applicant is correct in stating that the present application describes the production of several hybridomas, only one hybridoma is named in the

description (Example 2), hybridoma NFS-84B, deposited as ATCC Number HB983. Other hybridomas, disclosed to have been made in examples 3 to 57 and to produce monoclonal antibodies, are not named. The monoclonal antibodies allegedly produced by said hybridomas are not characterized or their utility demonstrated in the description.
Examples 3 to 57 disclose that various human tumour cells (also named in claim 7) were fused with fetal marrow cells (BG-231 or ATCC No. CRL 9835), lymphoblastoid cells (BM-95 or ATCC No. CRL 9832), or myeloma plasma cells (BA-160 or ATCC CRL 9834) "prepared according to Example 1". Example 1, pages 16 to 17, refers to these last three cell lines as "fusion cell lines", which produce immunoglobulins of class IgG, IgM and IgA respectively. Examples 3 to 57 name tumour cells and fusion lines, and state that fusion between a named tumour cell and fusion line resulted in a hybridoma producing a monoclonal antibody of a named immunoglobulin class, said monoclonal antibody reacting "with an idiotypic surface antigen". The description does not disclose any other features of said hybridomas or characterize the allegedly produced monoclonal antibodies. No names, deposit numbers, or details of binding activity and utility are disclosed for any of the hybridomas or monoclonal antibodies allegedly produced in examples 3-57.

The examiner's action of September 21, 2001 stated "Whether a monoclonal antibody produced by the method of the alleged invention will be IgG, IgM or IgA is selected by the fusion cell used and does not clearly identify or characterize any monoclonal antibody." Applicant's correspondence of March 19, 2002, stated:

> *"The Examiner suggested that the isotype of antibody produced by the hybridoma is selected by the fusion partner used. In fact, the isotype of the hybridoma is determined by the type of lymphocyte used to be fused with the fusion partner".*

The term "fusion partner" does not actually appear in the application. It seems that "the type of lymphocyte" means one of the fusion cell lines referred to in the preceding paragraph, as being disclosed on pages 16 and 17 of the description. In all examples, except for example 3, the resulting hybridoma secretes an antibody of the same class of immunoglobulin as the cell line (fetal marrow, lymphobastoid, or myeloma plasma cell) used for fusion. The description thus appears to indicate that the fusion line determines the class of immunoglobulin to which a monoclonal antibody made by the method of the invention will belong. The immunoglobulin class of the resultant monoclonal antibody is therefore known without making the monoclonal antibody, but other features of that antibody cannot be predicted.

Applicant's response of March 19, 2002, also stated that there is no requirement for there to be a deposit of all claimed cell lines, and that "the cell lines have been adequately described in term[s] of their specificity and the type of antibody that they produce." While a deposit does not replace adequate description of an alleged invention in the disclosure, a deposit of biological material made to an international depository authority supplements the description, and allows one skilled in the art to readily make and use the invention. Deposit information is disclosed in Example 2 for hybridoma NFS-84B and the monoclonal antibody produced by said hybridoma.

Each of the examples from 3 to 57 states that the resultant monoclonal antibody reacted "with an idiotypic surface antigen". No data is presented which indicates what said antigen is for any of the monoclonal antibodies in examples 3 to 57. Further, no data is presented which shows whether each of said monoclonal antibodies reacts specifically with the tumour cell to which the hybridoma producing a specific monoclonal antibody was raised. Example 2 at least discloses the molecular weight of the antigen which monoclonal antibody NFS-84B recognizes.

In its response to the Final Action, the Applicant stated, in part:

> The Examiner has issued a Final Action wherein the Examiner objects to claims 10 and 11 as being broader in scope than the teaching of the description. The Examiner asserts that while the description discloses hybridoma NFS-84B, it does not disclose any other identification or characterization of the monoclonal antibodies produced by the disclosed hybridoma or any other hybridoma. In particular, the Examiner argues that no names, deposit numbers, details of binding activity or utility or other features are disclosed for other monoclonal antibodies allegedly produced, such as in examples 3-57.

The Examiner cites the Decision of the Commissioner of Patents concerning Canadian Patent 1,338,323 (issued May 14, 1996), published in the Canadian Patent Reporter (CPR), Feb 4, 1998, Vol. 76 (3d), pages 206-218, wherein it states:

> *There was no description of the claimed hybridoma or any description of a method of preparing it. The only guidance was that they could be prepared by "traditional techniques". Although methods of making monoclonal antibodies to various antigens were known in the art, applying these methods to a new antigen constituted a new process requiring a new protocol to produce the secreting hybridomas and novel monoclonal antibodies specific to the antigen. The applicant could not rely on post-filing work by others to support its claims. The description did not include a clear reference or description to enable a person skilled in the art to make and use the invention without considerable and protracted experimentation.*

In our correspondence of March 19, 2002, we indicated to the Examiner how the above noted case was not applicable to the current application in that the above noted case fails to make <u>any</u> hybridomas or antibodies. In contrast, the present application specifically describes the production of several hybridomas and the production of monoclonal antibodies derived therefrom. In the present Office Action, the Examiner concurs, stating on page 2 that "the present application describes the production of several hybridomas". **To reiterate, the present application not only discloses the making of a variety of hybridomas but also the production of monoclonal antibodies from those hybridomas.**

At issue in the Decision published in 76 CPR (3d) 206 was whether the patent application provided sufficient disclosure to allow for "sound prediction" with respect to the claimed subject matter. It was decided that the principle of "sound prediction" was not applicable primarily because "the description did not include a clear reference or description to enable a person skilled in the art to make and use the invention without considerable and protracted experimentation. " In other words, they had a new retrovirus and claimed antibodies directed to region of the virus, however, they failed to disclose any method of making a hybridoma, any hybridoma or any monoclonal antibody produced therefrom. This is very different from the present case. In the current invention, the applicant provides a variety of hybridomas and isolated monoclonal antibodies therefrom. As a result, the concept of "sound prediction" is highly applicable in view of the explicitly written description. For example, the specification specifically discloses a protocol for making the antibodies on page 21, how to purify the antibodies on page 22, how to characterize SDS-PAGE electrophoresis and Western Blot immunoavidity studies on pages 8 and 23, and how to determine antibody binding on page 25. Such tests would enable one of ordinary skill in the art to determine the approximate size of the monoclonal antibody as well as its specific reactivity to idiotypic surface antigens on the tumour cells from which the hybridoma was produced. *See also* page 30, Example 2.

In view of the above, at this point we wish to draw attention to page 218 of CPR 76 (3d), wherein it states:

> *In the present case, the Applicant does not show by examples or broad statements the steps that were successfully used to produce hybridomas secreting monoclonal antibodies which are capable of binding only with the specific antigen. <u>Had any hybridoma and monoclonal antibody for certain antigens been prepared, then it would have been arguable that other hybridomas and monoclonal antibodies which were claimed but unprepared or prepared but untested, could be allowable in view of the "sound prediction" principle.</u> In this case there is no consideration given by the disclosure to any monoclonal antibody so that there is nothing upon which to base a sound prediction.*

The Board concluded that had any hybridomas and monoclonal antibodies been prepared, the "sound prediction" principle could have successfully been applied. The current application clearly provides an explicit example which is far more detailed than anything presented in the patent being discussed in the above noted case. **It is therefore respectfully submitted that the Decision of 76 CPR (3d) 206 in fact supports the present application in that the principle of "sound prediction" can be successfully applied due to the explicit description provided in the application.** The concept of "sound prediction" and its use in Canadian practice has been previously held to be acceptable in 65 CPR (2d) 73 (Ciba-Geigy AG v. Commissioner of Patents) wherein although the Commissioner of Patents felt that "the subject matter was

> untested and that the claims were speculative", under appeal, it was held that "the specification shows the predictability of the particular result".
>
> The Examiner has argued that claims 10 and 11 must be directed respectively to the use of a monoclonal antibody actually produced and to a composition comprising a monoclonal antibody actually produced. We disagree because the monoclonal antibody produced in either claims 10 and 11 will necessarily depend on the tumour cell used, such as those claimed in claim 7. This concept is further supported by the claims because claims 10 and 11 ultimately depend from claim 7. Therefore, using the principle of "sound prediction", and considering the detail provided in the Examples wherein described is the production of various antibodies from various hybridomas, it is respectfully requested that the Examiner reconsider the objection to claims 10 and 11.

Both the Examiner and the Applicant have referred to the Decision of the Commissioner of Patents concerning the application which issued as Canadian Patent No. 1,338,323 (hereinafter "Pasteur", published as *Institut Pasteur Application* 76 C.P.R. (3d) 206).

In "Pasteur", the Commissioner refused to grant a patent with claims to a monoclonal antibody and a hybridoma. The Decision reads, in part:

> .... the Applicant does not show by examples or broad statements the steps that were successfully used to produce hybridomas secreting monoclonal antibodies that are capable of binding only with the specific antigen. Had any hybridomas and monoclonal antibody for certain antigens been prepared, then it would have been arguable that other hybridomas and monoclonal antibodies, which were claimed but unprepared or prepared but untested, could be allowable in view of the "sound prediction" principle. In this case there is no consideration given by the disclosure to any monoclonal antibody so that there is nothing upon which to base a sound prediction. The Board finds that there is a lack of guidance in describing the core method to be used and the permissible modifications of that basic method for the specific antigens disclosed.

The "Pasteur" application neither described hybridomas nor a "core method" for preparing these. By contrast, the instant application includes a detailed procedure for preparing a human-human hybridoma secreting a monoclonal antibody. Example 1 describes the preparation of a human tumour cell/spleen cell suspension, the sensitization of the spleen cells prior to fusion with human B lymphocytes, the lymphocyte fusion lines, the fusion step, hybridoma screening, and antibody production, purification and characterization. The procedure of example 1 is the "core method" for preparing hybridomas and monoclonal antibodies.

Example 2, describes the preparation of hybridoma NFS-84B (deposited with the ATCC under no. HB893) using the method of example 1. Examples 3 through 57 disclose the preparation of 55 other hydridomas using the "core method".

Clearly, the instant application is different from that which led to the "Pasteur" decision. However, the Examiner has cited "Pasteur" to argue that hybridomas that lack a "specific description"cannot be claimed. The Examiner contends that only hybridoma NFS-84B (example 2) is <u>specifically described</u> since it is named and "deposited", and thus claims 10 and 11 must be restricted to the monoclonal antibody produced by this hybridoma.

Subsection 34(1) of the Patent Act as it read immediately before October 1, 1989 states:

> An applicant shall in the specification of his invention
> (a) ....
> (b) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture, or composition of matter, in such full, clear, concise and exact terms as to enable any person skilled in the art or science to which it appertains, or with which it is most closely connected, to make, construct, compound or use it;
> (c) ....

Section 38.1 of the Act provides for a deposit of biological material to be considered as part of the specification and taken into consideration in determining if Subsection 34(1) of the Act has been complied with. A deposit can therefore be used to supplement the written description of the invention where the requirements of Subsection 34(1) of the Act cannot be complied with by words alone.

In the instant application, the Applicant has disclosed an allegedly novel method for preparing human-human hybridomas secreting monoclonal antibodies. Fifty-six examples are provided where hybridomas were prepared according to the method. Each hybridoma is described in terms of the tumour and spleen cells which were mixed together, a fusion line, and class of monoclonal antibody secreted. Each example states that the antibody reacts with an idiotypic surface antigen. Each type of tumor cell listed in claim 7 is used in at least one of the examples.

The Board is satisfied that the Applicant has described its hybridomas and their method of preparation in sufficient detail that one of skill in the art could practice the invention without a reference to a biological deposit. The Board does not agree that claims 10 and 11 are broader in scope than the teachings of the description and must be restricted to hybridoma NFS-84B.

The Board therefore recommends that the Examiner's rejection of claims 10 and 11 be reversed and the application be returned to the Examiner for further prosecution.

M. Gillen	M. Wilson	J. Cavar
Chairman	Member	Member

I concur with the recommendation of the Board that the Examiner's rejection of claims 10 and 11 be reversed and that the application be returned to the Examiner for further prosecution.

David Tobin
Commissioner of Patents

Dated at Gatineau, Quebec,
this 29th day of November, 2006