COMMISSIONER'S DECISION SUMMARY

C.D. 1206 ....Application No. 529,362 (B20, B22, C00)

Claims rejected as being broader than the disclosure

The examiner rejected certain claims of the application on the grounds that they were broader than the invention disclosed since they claimed the preparation of monoclonal antibodies the preparation of which had not been adequately disclosed. The Board ruled that the claims had been properly rejected and recommended that the rejection be upheld.

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 529,362, having been rejected under Subsection 47(2) of the Patent Rules, the Applicant asked that the Final Action of the Examiner be reviewed. The rejection has consequently been considered by the Patent Appeal Board and by the Commissioner of Patents. The findings of the Board and the ruling of the Commissioner are as follows:

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This decision deals with the Applicant's request that the Commissioner of Patents review the Examiner's Final Action on patent application number 529,362 (Class 195-1.105) filed on February 10, 1987 for an invention entitled "NEW RETROVIRUS CAPABLE OF CAUSING AIDS, MEANS AND METHODS FOR DETECTING IT IN VITRO". The inventors are Luc Montagnier; Solange Chamaret; Denise Guetard; Marc Alizon; François Clavel; Mireille Guyader; Pierre Sonigo; Françoise Brun-Vezinet; Marianne Rey; Christine Rouzioux and Christine Katlama and the application is assigned to Institut Pasteur. The Examiner in charge of the application issued the Final Action on October 8, 1993 refusing claims 11 to 34, 40, 43 to 54 and 70 and, by implication, declaring claims 1 to 10, 35 to 39, 41, 42, 55 to 69 and 71 to 73 to be allowable.

The Applicant replied on April 8, 1994 requesting a review by the Commissioner of Patents and an oral hearing before the Patent Appeal Board. Consequently an oral hearing was held on January 18, 1995 at which Denise Huberdeau, Danielle Banerman and Stéphane Drouin represented the Applicant. Drs. Isaac Ho and Linda Brewer represented the Patent Branch and the Board was comprised of Peter Davies as Chairman and Drs. Michael Howarth and Effat Maher as members.

The application, as outlined in the abstract, relates to a new class of retrovirus named HIV-2; to antigens obtained from this virus, namely proteins p12, p16, p26 and glycoprotein gp140, and to immunogenic compositions containing these antigens, particularly glycoprotein gp140. The antigens are used for the in vitro diagnosis in man for potentiality of certain forms of AIDS. The application also relates to the application of cloned DNA sequences derived from the RNA of HIV-2 as probes in diagnostic kits.

In her Final Action, the Examiner rejected claims 11 to 16, 21, 34, 40, 47, 52, 53, 54 and 70 of the application under Subsection 34(2) of the Patent Act as being indefinite and not supported by the disclosure. The Examiner also rejected claims 11 to 33 and 43 to 51 under Subsection 39(1) of the Act.

In its response dated April 8, 1994 the Applicant submitted a new set of claims comprising claims 1 to 93 for consideration by the Board and on January 17, 1995, immediately prior to the oral hearing, a further set of claims making minor, mostly editorial changes to the claims previously submitted. Since the claims submitted on January 17, 1995 are similar to those submitted on April 8, 1994 the Board has decided to consider the latter set of

claims in this decision but sees no reason why the former set of claims may not be considered by the Examiner at the conclusion of these proceedings.

In arguing against the rejection of claims 11 to 29 and 55 to 66 (former claims 11 to 33 and 43 to 51) under Subsection 39(1) of the Act, the Applicant stated that the claims were directed to compounds used as diagnostic agents rather than as medicines and as such did not fall within the scope of the Subsection. The Board accepts this argument as persuasive in overcoming the rejection and recommends that the rejection based on these grounds be withdrawn. Furthermore after reviewing the claims submitted on April 8, 1994 the Board is satisfied that claims 1 to 60, 67 to 83 and 86 to 93 avoid the objections made by the Examiner leaving only claims 61 to 66, 84 and 85 under rejection. Accordingly the oral hearing was limited to argument directed towards claims 61 to 66, 84 and 85 only.

Subsequent to a discussion held during the oral hearing the Applicant, on February 10, 1995, filed an amended set of claims 61 to 66 which, in the Board's opinion, overcome the Examiner's objection to the claims; the Board therefore recommends that the amended claims be accepted as allowable.

The only remaining claims under rejection are therefore claims 84 and 85 and the remainder of this decision will be addressed to these claims which are as follows:

Claim 84 Antibody according to any one of claims 78 to 83, characterized in that it is monoclonal.

Claim 85 The hybridoma secreting the monoclonal antibody according to claim 84.

In the Final Action, the Examiner rejected claim 53 (now claim 84) directed to a monoclonal antibody and claim 70 (now claim 85) directed to the hybridoma secreting the monoclonal antibodies stating the following:

> Objection to claims 53 and 70 (previously 49 and 66, respectively) for lack of specific support in the disclosure is maintained. Applicant has not prepared any hybridomas or monoclonal antibodies. Applicant has suggested that monoclonal antibodies are a reasonable extension of the alleged invention and that the crucial inventive step in the preparation of monoclonal antibodies lies in obtaining the antigens to which these antibodies bind. Applicant has argued that specific exemplary support would simply consist of including in the disclosure, standard procedures for hybridoma and monoclonal antibody preparation.
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> The examiner agrees that once an antigen is available, a hybridoma and a monoclonal antibody can be prepared using well established techniques. While the path to a monoclonal antibody may be obvious, the product of that path is not

> obvious. If it were, there would be nothing inventive about the product. A product cannot be both obvious and inventive at the same time. Applicant has not prepared a hybridoma or a monoclonal antibody. Applicant is claiming something that he cannot describe in terms of a structure, or in terms of physical or chemical properties. He is, in fact, claiming hoped-for products which have been described only in terms of a biological activity or utility. The disclosure of a patent application is addressed to one skilled in the art to which the invention relates and must be written such that one skilled in the art would be able to put the invention to the same successful use as the inventor. Applicant has not shown that he was successful in the production of hybridomas or monoclonal antibodies and therefore fails to provide sufficient support for claims to these products.

The questions before the Board are whether or not the specification describes correctly and fully the preparation and the properties of the hybridoma and the monoclonal antibodies claimed in claims 84 and 85, and whether or not such description is set out in such clear concise terms as to enable a person skilled in the art to make and use the invention as required by Subsection 34.(1) of the Patent Act which reads as follows:

> An applicant shall in the specification of his invention
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> (a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;
>
> (b) set out clearly and fully 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;
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> (c) in the case of a machine, explain the principle thereof and the best mode in which he has contemplated the application of that principle;
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> (d) in the case of a process, explain the necessary sequence, if any, of the various steps, so as to distinguish the invention from other inventions; and
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> (e) particularly indicate and distinctly claim the part, improvement or combination that he claims as his invention.
> (Emphasis added)

In the present case, the question with regard to Subsection 34.(1)(a) is whether the written description of the application provides sufficient detailed information for any person skilled in the art to produce and characterize the claimed monoclonal antibodies and the hybridomas secreting such antibodies. The Board finds that the only guidance or direction given for the preparation of the embodiments of claims 84 and 85 in the specification is that given on page 50 of the disclosure as follows:

> . . . It [the invention] also relates to the monoclonal antibodies which can be produced by traditional techniques, these monoclonal antibodies being directed, respectively, more specifically against the different proteins of HIV-2.

> These polyclonal or monoclonal antibodies can be used in different applications. Their use for neutralizing the corresponding proteins, or even inhibiting the infectivity of the whole virus, will mainly be mentioned. They can also be used, for example, for demonstrating the viral antigens in biological preparations or for carrying out procedures for purification of the corresponding proteins and/or glycoproteins, for example by using them in affinity chromatography columns.

The Board cannot find any description of the hybridoma of claim 85 or any description of a method of preparing it provided in the above cited statements or in the entire description. No specific description of the monoclonal antibodies in claim 84 or a process for their preparation is disclosed. The only guidance as to the description of the monoclonal antibodies and the process by which they may be prepared is that they can be prepared by "traditional techniques." The sole specific technical teaching provided is the identity of the antigens. Describing and identifying the antigens does not provide support for the hybridoma or the monoclonal antibodies nor does it provide sufficient instruction on how to make the antibodies.

The Applicant's description of the monoclonal antibodies as neutralizing or binding with the antigens is not considered a specific description. The term antibody denotes a material that opposes and neutralizes a body; in this case, the body is the antigen. An antibody must fit and bind with a particular antigen otherwise it would not be called an antibody. The antibody is expected to have the property of binding to the antigen because it is presumed to be an antibody for that antigen. The Applicant's description makes an unwarranted assumption, taking for granted what really needs to be accomplished and supported by its specification.

The requirement under Subsection 34.(1)*(b)* is that the specification present the invention in such clear, exact and concise terms as to enable one of ordinary skill in the art to make and use the invention with the same success as the inventor. In R.C.A. Photophone, Ld. v. Gaumont-British Picture Corporation, Ld. and British Acoustic Films, Ld. (1936) 53 R.P.C. 167, Lord Justice Romer stated, at page 195, that:

> . . . It is the duty of a patentee by his claim to make quite clear what is the ambit of his monopoly in order that workers in the art may be left in no doubt as to the territory that is forbidden them during the life of the patent. If he fails to do this, his patent becomes a public nuisance. It is equally incumbent upon him to describe at least one way, and the best way known to him, of carrying his invention into effect, in order that, when his monopoly comes to an end, the workers in the art may turn the invention to account. This is the consideration he pays for his monopoly.

The Applicant has argued that it was standard procedure to prepare hybridomas and monoclonal antibodies for antigens at the date of filing the application. This argument was developed by the Applicant in its response of April 8, 1994, at page 18, as follows:

> The fundamental aspect of the invention is, as the Examiner has stated in the final action, the HIV-2 virus and its antigens. Once the antigens have been identified and characterized, it is submitted that:
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> (1) the path to the preparation of the monoclonal antibodies is an easy one for those skilled in the art, and
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> (2) the resulting antibodies will have the desired immunogenic character.
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> As stated at page 50 of the specification, to produce antibodies, an immunogenic substance (such as an HIV-2 antigen) is injected to an animal (usually a rabbit, a guinea pig or a sheep) to produce polyclonal antibodies. Monoclonal antibodies can then by [sic] produced using traditional techniques. What constituted a traditional technique for producing monoclonal antibodies as of Applicant's priority date of January 22, 1986? For example, lymphocyte cells from the immunized animals producing antibodies to the injected immunogen are fused to myeloma cells. The resulting hybrid cells are inoculated in the peritoneal cavity of syngeneic hosts. This results in the formation of tumors (hybridomas) that secrete high concentrations of monoclonal antibodies in the sera or ascites fluids. Such technique was well-known to the person skilled in the art way before the priority date of January 22, 1986 as it is demonstrated below.

The Applicant then presented a brief review of the state of the art in preparing hybridomas and monoclonal antibodies starting with the work of Kohler and Milstein in 1975.

The Board acknowledges that methods of making monoclonal antibodies to various antigens were known in the art at this date; however applying these methods to a new antigen constitutes a new process requiring a new protocol to produce the secreting hybridomas and novel monoclonal antibodies specific to the antigen.

James W. Goding, in *"Antibody Production By Hybridomas"*, Journal of Immunological Methods, Volume 39, page 286 (1980) comments on the nature of this type of work as follows:

> . . . It should be stressed that the production, testing, cloning and characterisation of monoclonal antibodies is not a trivial procedure. It should not be undertaken without an appreciation that it will involve some months of fairly continuous bench work.

To understand the general concept of the physiology and the biochemistry of antigens, antibodies, hybridomas and monoclonal antibodies, the following is an outline from the book Monoclonal Antibodies by Karol Sikora & Howard M. Smedley, 1984 published by Blackwell Scientific Publications, page 3:

> Many molecules are capable of giving rise to an immune response, i.e. they are antigens. Each molecule has a unique shape. It is this shape which gives rise to the specificity of an antigen-antibody reaction. Clearly larger and more complex molecules may have several different regions, each of which is capable of accommodating an antibody. Such regions are known as antigenic determinants or epitopes. It is possible for one antigenic molecule to contain several epitopes. Smaller antigens, on the other hand, may possess only one epitope. The basis of the antibody-antigen interaction is the fitting together of two molecules of complementary shape. The shape of the antigen is determined by the three dimensional structure of the molecule. All immunoglobulin molecules [antibodies] have a similar basic structure consisting of two heavy and two light chains held together by disulphide bonds.

(An antigenic epitope fits and binds at the binding site between the N terminal of a pair of a light and a heavy chains.)

On page 8, the authors continue:

> Although the fusion techniques outlined above enable antibodies of defined specificity to be produced in endless quantities, it should be stressed right from the beginning that for every successful antibody which is produced many failed fusions or irrelevant monoclonals will be produced. Many hours of laboratory time are spent to produce a single useful MCA [monoclonal antibody]. Some of the reasons for this are obvious. First of all the definition of what is a "good" monoclonal antibody is arbitrary and depends upon what function is required of it by the investigator. . . . It is therefore important for an investigator to know what he requires of his antibody before deciding which antibodies are good or bad. Further, many antigens against which the investigator is attempting to raise monoclonal antibodies are only weakly immunogenic. The animal's immune system therefore responds poorly to the immunogen and so the incidence of suitable monoclonals is low, thus increasing the workload.

The state of the art at the approximate time of filing the application (1987) can also be estimated from Goding in his book Monoclonal Antibodies: Principles and Practice, Second edition, 1986, Academic Press. On page 281, in writing about the creation of conventional [polyclonal] antibodies, the author states:

> The production of monoclonal antibodies involves a great deal of work. A suitable screening assay must be developed before the fusion, and hundreds or thousands of tests will have to be performed before the prized clone is immortalized. The sheer work and time involved in "cell farming" is considerable. In comparison, the preparation of antibodies with nothing more than antigen, a rabbit, and a syringe, might be seen as a technological breakthrough! For many purposes, conventional antibodies will do the job adequately, with much less work.

On page 3, Goding explains:

> It would be wrong to think that monoclonal antibodies will completely replace conventional serology. The production of monoclonal antibodies involves a great deal of work, and a high level of commitment. There will often be occasions when the effort required may not be justified. Fortunately, a wide range of monoclonal antibodies is becoming commercially available.
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> . . . I have also tried to point out areas in which the literature gives misleading impressions, and a few situations in which published procedures are unreliable.

> . . . Immunochemistry also has an oral tradition, and a surprising number of key elements are not easily accessible from the literature. I have incorporated some of the elements where appropriate; in many cases no citation is possible.

On page 59, in the Chapter titled *"Production of Monoclonal Antibodies"*, Goding adds:

> Although the technology of hybridoma production is now firmly established, there are a large number of steps involved, and each of these may be carried out in many different ways. The diversity of published approaches reflects both individual biological problems and previous experience. The methods also vary in convenience, speed, reliability and expense, but there is no one "right" approach, and ultimately each investigator must choose and adapt the published strategies to individual needs. An appreciation of the variables and compromises will help minimize the effort required.

It is clear from the above remarks by Goding that a person skilled in the art must establish a specific protocol to produce the hybridomas and the monoclonal antibodies for each of the antigens. In exercising his skill, the expert would not depend entirely on the articles and textbooks in the field or "traditional techniques", as a number of key elements are not easily accessible from the literature. If the preparation of monoclonal antibodies to antigens were routine and predictable, then all monoclonal antibodies to antigens would be obvious, and the field of immunology would routinely produce all kinds of cures. This is certainly not the case.

The Board agrees with the U.S. decision in Ex Parte Old 229 USPQ 197 (Bd. Pat. App. 1985), which states, on page 200, that:

> . . . Although the technique underlying hybridoma technology is well recognized, nevertheless, the results obtained by its use clearly are unpredictable. Hybridoma technology is an empirical art in which the routineer is unable to foresee what particular antibodies will be produced and which specific surface antigens recognized by them. Only by actually carrying out the requisite steps can the nature of the monoclonal antibodies be determined and ascertained; no "expected" results can thus be said to be present.

The Applicant submitted two published papers during the oral hearing, namely: *"Two Neutralizing Domains in the V3 Region in the Envelope Glycoprotein gp125 of HIV Type 2"*, by Ewa Björling et al., published by The American Association Of Immunologists in 1994; and *"Multiple Antigenic Epitopes Expressed on gag Proteins, p26 and p15, of a Human Immunodeficiency Virus (HIV) Type 2 as Defined with a Library of Monoclonal Antibodies"*, by Hiroyoshi Komatsu et al. which was published in 1990 in Aids Research and Human Retroviruses, Volume 6, Number 7, by Mary Ann Liebert, Inc., Publishers. The Applicant argues that these papers disclose the preparation of monoclonal antibodies using the

subject antigens and this fact proves that preparing the hybridoma and monoclonal antibodies are a standard procedure such that claims 84 and 85 cannot be rejected for lack of disclosure.

It is the Board's opinion that the Applicant cannot rely on post-filing work by others to support its claims. The Board agrees with the U.S. decision in Re Glass, 181 USPQ 31 (C.C.P.A. 1974) that sufficiency of support is measured as of the date the application is filed, and that post-filing publications cannot be used to fill in what is missing from the teaching of how to make and use the claimed invention. Furthermore, the Board concurs with the U.S. decision in Gould v. Quigg, 3 USPQ2d 1302 (Fed. Cir. 1987) that post-filing publications may be used to show that the invention, as described in the application when filed, was operable.

In a further argument, the Applicant urged the Board to follow, by analogy, the practice followed in the chemical arts. Thus at page 23 of the response dated April 8, 1994 it is stated that:

> In a patent application disclosing an invention in the chemical arts, an applicant usually provides general comments on the type of compounds of interest with specific examples to compounds belonging to the generic class. This Applicant may describe a way in which derivatives or other embodiments which might be quite different from the specific compounds disclosed can be prepared. Claims to these compounds are usually added and allowed by the Patent Office. This type of situation is perfectly in line with the decision of the Supreme Court of Canada in Monsanto v. the Commissioner of Patents (1979 2CPR 2d 161) in which Mr. Justice Pigeon made the following comments:
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> > *"In my opinion, the Commissioner cannot refuse a patent because the inventor has not fully tested and proved it in all its claimed application. This is what he has done in this case by refusing to allow claims 9 and 16 unless restrictive to what had been tested and proved before the application was filed. If the inventors have claimed more than what they have invented in included substances which are devoid of utility, the claims will be open to attack. But in order to succeed, such attack will have to be supported by evidence of lack of utility. At present, there is no such evidence and there is no evidence that the production for utility of every compound named is not sound? [sic] and reasonable."*

and at page 25 :

> According to the Supreme Court in the Monsanto decision referred to above (c.f. supra), a "sound-prediction" is based on the capacity of the person skilled in the art to foresee the properties of a claimed product. Applicant has demonstrated that techniques to produce monoclonal antibodies have become tools generally available to a person skilled in the art of hybridoma technology, in the same way the preparation of specific chemical compounds from a generic formula based on known processes is available to the person skilled in the art of chemical synthesis.

In the Monsanto case referred to by the Applicant the application disclosed a class of chemical compounds which inhibit the premature vulcanization of diene rubbers. The inventors gave the

common formula for the nucleus of the substances and described various radicals which could be used in the class. Three representative compounds were disclosed, but many more compounds were not disclosed yet were claimed. The specification described the preparation of the three compounds specifically, while the preparation of the other compounds was described generally by formula.

It was recognized in Monsanto's application that the disclosure provided sufficient direction to enable a skilled chemist to prepare the compounds using methods previously known in the art but it was determined that since the inventor had not prepared and tested all of the claimed compounds it could not be fairly said that the inventor had invented all of the claimed compounds. The rejected claims were however later found allowable by the Supreme Court on the grounds that there was no evidence that either the compounds not prepared or tested would not work in view of the disclosed examples of compounds prepared and tested.

Thus in Monsanto 42 C.P.R. (2d) 161 the Supreme Court, at page 175, referred to the judgment in Olin Mathieson Chemical Corp. v. Biorex Laboratories Ltd. [1970] R.P.C. 157. In Olin Mathieson, the patent covered trifluoromethyl-phenothiazine and a number of related compounds, of which a small number only had been tested. The question was then whether the inventor ought to be limited to the actual substances which he had tested. On page 193, Mr. Justice Graham defined sound prediction as follows:

> Where, then, is the line to be drawn between a claim which goes beyond the consideration and one which equiparates with it? In my judgment this line was drawn properly by Sir Lionel when he very helpfully stated in the words quoted above that it depended upon whether or not it was possible to make a sound prediction. If it is possible for the patentee to make a sound prediction and to frame a claim which does not go beyond the limits within which the prediction remains sound, then he is entitled to do so. Of course, in so doing he takes the risk that a defendant may be able to show that his prediction is unsound or that some bodies falling within the words he has used have no utility or are old or obvious or that some promise he has made in his specification is false in a material respect; but if, when attacked, he survives this risk successfully, then his claim does not go beyond the consideration given by his disclosure, his claim is fairly based on such disclosure in these respects, and is valid.
> (Emphasis added)

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. 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. 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. Such deficiencies in guidance cannot be remedied by referring the person skilled in the art to experiment with the "traditional techniques."

In summary, the Board also finds that the description does not include any clear references or description to enable the person skilled in the art to make and use the invention without considerable and protracted experimentation. The Board concludes that the hybridomas and the monoclonal antibodies embraced by the claims 84 and 85 are not described or enabled by the present disclosure as required under Subsection 34(1) of the Patent Act. Accordingly the Board recommends that the Examiner's refusal of claims 84 and 85 be upheld.

Peter J. Davies	Effat Maher	Michael Howarth
Acting Chairman	Member	Member

I concur with the findings and recommendations of the Board. I am satisfied that the Applicant is not by law entitled to be granted a patent containing claims 84 and 85 and I therefore refuse to grant a patent containing these claims on this application.

M. Leesti
Commissioner of Patents

Dated at Hull, Quebec
this 11th day of December 1995