Commissioner=s Decision # 1296
Décision de la Commissaire # 1296

TOPIC: B22, F00, O00
SUJET: B22, F00, O00

Application No. : 2,072,017
Demande n^{o} : 2,072,017

Commissioner=s Decision Summary

The subject application was rejected in a Final Action mainly for two reasons: (i) lack of support for claims related to genetically engineered antibodies (chimeric and humanized antibodies); and (ii) lack of novelty of claims related to murine antibodies. The claim-set submitted in response to the Final Action appeared to have avoided the prior art cited for lack of novelty; however, the question of obviousness arose. The question of support for genetically engineered antibodies in the new claim-set remained. It was found that there was adequate support for chimeric antibodies but not for humanized antibodies and that the subject matter of the new claim-set was neither anticipated nor obvious. The Board recommended that certain amendments be required in order to render the application compliant with the Act and Rules. The Commissioner of Patents agreed with the Board and the Applicant was invited to make the required amendments failing which the application would be refused.

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,072,017 having been rejected under Subsection 30(4) of the *Patent Rules*, has consequently been reviewed in accordance with Subsection 30(6) of the *Patent Rules* by the Patent Appeal Board on behalf of the Commissioner of Patents. The findings of the Board and the ruling of the Commissioner are as follows:

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INTRODUCTION

[1] This decision deals with a review pursuant to subsection 30(6) of the *Patent Rules* of a Final Action taken under subsection 30(4) of the *Patent Rules* on patent application 2,072,017.

[2] The Applicant is the Sloan-Kettering Institute for Cancer Research and the invention is entitled ATHERAPEUTIC USES OF THE HYPERVARIABLE REGION OF MONOCLONAL ANTIBODY M195 AND CONSTRUCTS THEREOF.@ The inventor is David A. Scheinberg.

PROSECUTION HISTORY

[3] The subject application was filed on December 14, 1990 and examination was requested on December 8, 1997. A series of reports and responses ensued, culminating in the issuance of a Final Action on August 28, 2007, at which time all 31 claims in the application were variously rejected for lack of novelty under paragraph 28.2(1)(a) of the *Patent Act*, lack of support under subsection 138(2) of the *Patent Rules*, and ostensibly for failure to comply with paragraph 80(1)(f) of the *Patent Rules*.

[4] The Applicant responded to the Final Action on February 28, 2008 by filing a new set of 42 claims and by submitting that the new claim-set was compliant with the *Patent Act* and with the *Patent Rules*. Since the Examiner found that the amendments did not overcome the defects set forth in the Final Action, the application was referred to the Board for review.

[5] The Applicant was invited by the Board to present additional submissions at a hearing but declined to do so. At the time of the hearing invitation the Board also alerted the Applicant to several post-Final Action developments. In order to address these developments the Applicant was offered the opportunity to consider and provide submissions on: comments made by the examiner on the new claim-set made in a Summary of Reasons provided to the Board; the effect, if any, of the Supreme Court=s decision regarding anticipation and obviousness in *Sanofi-Synthelabo Canada Inc. v. Apotex Inc.*, 2008 SCC 61, 69 C.P.R. (4th) 251 [*Sanofi*]; and the publication of revised biotechnology practice guidelines (Chapter 17 of the *Manual of Patent Office Practice* revised January 2009). No submissions were received.

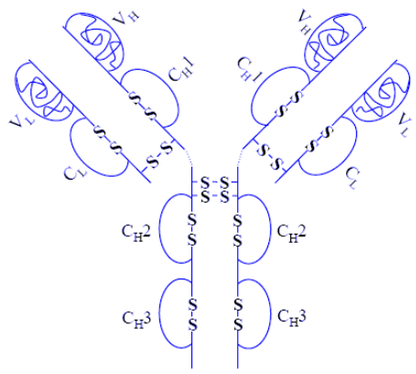
BACKGROUND

Antibody Structure and Engineering

[6] The invention relates to antibodies; more particularly, therapeutic monoclonal antibodies for treating leukemia. An overview of mammalian monoclonal antibody technology will be helpful to the present review.

[7] Antibodies are proteins which specifically bind to foreign antigens and are produced by B cells of the immune system in response to exposure to the foreign antigen. In addition to their antigen binding function, antibodies are also able to effect certain physiological functions, such as complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) in which cells that have been targeted for destruction through binding of an antibody to an antigen found on the surface of the cell are destroyed by immune system cells. There are five different types of antibody molecules, of which the IgG type is typical. IgG antibodies are AY@

shaped molecules made up of four polypeptide chains (two identical Aheavy@ chains joined together at a hinge region and two identical Alight@ chains) which link together to form a complete molecule. The following graphic (publically available from Wikimedia Commons) depicts a complete IgG molecule:



[8] As shown above, the heavy and light chains of an antibody each carry two types of regions: Avariable@ regions (labelled AV_H@ and AV_L@); and Aconstant@ regions (labelled AC_H1@, AC_H2@, AC_H3@ and AC_L@). A heavy chain has three constant regions and one variable region whereas a light chain has one of each. Variable and constant regions within the light and heavy chains are each joined together by a short AJ@ region (not shown), with the heavy chain further including a short AD@ region (not shown). Proteolytic cleavage near the hinge region of an IgG antibody with pepsin or papain releases antigen-binding fragments termed AF(ab=)$_2$ fragments@ and AFab fragments,@ respectively.

[9] The variable regions are responsible for providing the molecule with its binding function through the provision of antigen binding sites found at the tips of the variable regions. The antigen binding sites within the variable regions are themselves primarily formed through the interaction of short stretches of amino acids located in six hypervariable regions (also known as Acomplementarity determining regions@ or ACDRs@). While termed Avariable@, the variable regions have relatively conserved framework regions whereas the hypervariable regions have unpredictable amino acid sequences.

[10] The constant region is responsible for providing effector function (such as ADCC) to the molecule.

[11] Murine antibodies may be altered, or engineered, to avoid unwanted side-effects when used therapeutically and/or to take advantage of the differing functionalities conferred on murine antibodies when their constant regions are replaced with human ones. For instance, a murine monoclonal antibody may have certain desirable antigen binding characteristics but may suffer from the drawback of being unable to effect cell-mediated killing of cells in human patients because of its murine constant region, which is not completely compatible with the patient=s cellular immune system. Furthermore, since the human immune system would recognize a murine antibody as a foreign antigen, such antibodies can trigger an undesirable human anti-mouse antibody immune response (HAMA).

[12] One antibody engineering strategy involves excising the whole of the murine variable regions from the murine antibody and attaching them to a human constant region. For the sake of

the present review we will call these antibodies Achimeric@ antibodies since they possess parts of murine and human antibodies. Chimeric antibodies, being more human-like, are less likely to trigger a HAMA response in patients.

[13] A second, more refined and sophisticated antibody engineering strategy essentially involves transplanting the murine amino acid sequences of the critical hypervariable regions onto human variable region frameworks (along with their attendant human constant regions). For the sake of the present review we will call these antibodies Ahumanized@ antibodies. Although not fully Ahuman@ these antibodies are more human-like than chimeric antibodies and consequently go that much further towards reducing HAMA in patients.

[14] Humanized and chimeric antibodies take further advantage of the cell-effector functions provided by a human constant region, which is fully compatible with a patient=s cellular immune system.

[15] Although the present specification seems to indicate that Ahumanized@ antibodies are a preferred subtype of more generic Achimeric@ antibodies (see page 20, lines 23-24 and compare to page 19, lines 14-15 which states AA chimeric antibody is one in which portions of the antibody are derived from two or more different organisms@), we consider it appropriate, in view of the terminology commonly used in the art (see for example *Morrison* and *Borrebaeck*, *infra*), to distinguish between the two types and treat them as distinct, yet related, products.

The Invention

[16] The present invention is concerned with antibodies directed to a cell surface antigen, termed CD33, which is found on leukemic cells. The human CD33 antigen is not recognized as foreign in humans and hence it is difficult to generate fully human antibodies capable of targeting this antigen. However, inventor Scheinberg was able to generate a monoclonal antibody to the CD33 antigen by first immunizing mice and then performing classical monoclonal antibody production techniques. The resultant particular murine monoclonal antibody discussed throughout the specification is termed AM195@ and is produced by a hybridoma cell line deposited with the American Type Culture Collection (ATCC) under accession number HB 10306.

[17] The present specification seeks, or proposes, to optimize the therapeutic utility of the murine M195 antibody by engineering it in order to generate chimeric and humanized versions. The specification also goes on to describe therapeutic agents having a cytotoxic agent conjugated to the M195 antibody or its derivatives; i.e., so-called Amagic bullets@ which are capable of selectively eliminating leukemic cells.

THE CLAIMS

[18] In response to the Final Action the Applicant submitted a new set of 42 claims which differed from the claim-set before the Examiner at the time the Final Action was written. This new claim-set includes the following representative claims:

1. An antibody or antigen-binding fragment thereof, other than murine monoclonal antibody M195 (ATCC No. HB 10306), comprising an amino acid sequence capable of specifically binding to the epitope to which monoclonal antibody M195 binds.

2. The antibody of claim 1, wherein the amino acid sequence comprises the amino acids of the hypervariable regions of monoclonal antibody M195 (ATCC No. HB 10306) necessary for binding to the epitope.

3. The antibody of claim 2, wherein the amino acid sequence of the hypervariable regions is the same as the amino acid sequence of the hypervariable regions of monoclonal antibody M195 (ATCC No. HB 10306).

4. The antibody of claim 3, wherein the antibody further comprises a human immunoglobulin constant region.

5. The antibody of claim 4, which antibody is a humanized antibody.

6. The antibody of claim 5, which antibody is a dimeric antibody comprising two intact antibodies linked together.

7. A therapeutic agent which comprises the antibody of claim 5 and a cytotoxic conjugated thereto.

8. A pharmaceutical composition which comprises an amount of the therapeutic agent of claim 7 effective to treat leukemia and a pharmaceutically acceptable carrier.

20. A therapeutic agent comprising humanized monoclonal antibody M195 (ATCC HB 10306) and a cytotoxic agent conjugated thereto, wherein the cytotoxic agent is a polypeptide toxin.

21. A therapeutic agent comprising humanized monoclonal antibody M195 (ATCC HB 10306) and a cytotoxic agent conjugated thereto, wherein the cytotoxic agent is an alpha particle emitter.

25. A therapeutic agent comprising humanized monoclonal antibody M195 (ATCC HB 10306) and a cytotoxic agent conjugated thereto, wherein the cytotoxic agent is a beta particle emitter selected from the group consisting of Scandium-47, Rhenium-186, Rhenium-1 88, and Yttrium-90.

28. A therapeutic agent comprising humanized monoclonal antibody M195 (ATCC HB 10306) and a cytotoxic agent conjugated thereto, wherein the cytotoxic agent is an auger electron generator selected from the group consisting of lodine-123, Bromine-77, and Indium-111.

30. A therapeutic agent comprising humanized monoclonal antibody M195 (ATCC HB 10306) and a cytotoxic agent conjugated thereto, wherein the cytotoxic agent is a fissionable nuclide selected from the group consisting of Boron-10 and an Actinide.

31. Use of a therapeutic agent comprising humanized monoclonal antibody M195 (ATCC HB 10306) and a cytotoxic agent conjugated thereto in the manufacture of a medicament for treating acute or chronic myeloid leukemia in a human patient.

32. Use of a therapeutic agent comprising humanized monoclonal antibody M195 (ATCC HB 10306) and a cytotoxic agent conjugated thereto for treating acute or chronic myeloid leukemia in a human patient.

39. Use of a therapeutic agent comprising humanized monoclonal antibody M195 (ATCC HB 10306) and a cytotoxic agent conjugated thereto in the manufacture of a medicament for destroying a human myeloid leukemia patient's bone marrow cells.

40. Use of a therapeutic agent comprising humanized monoclonal antibody M195 (ATCC HB 10306) and a cytotoxic agent conjugated thereto for destroying a human myeloid leukemia patient's bone marrow cells.

THE ISSUES

[19] In our view the Final Action raises two main questions:

(1) To what extent does the present specification support the claimed antibodies and conjugates thereof?

(2) Is the claimed subject matter free of the prior art?

ISSUE NO. 1: SUPPORT FOR ANTIBODIES AND CONJUGATES

[20] Based on the claim-set now on file, the first main question requires us to consider whether there is adequate support for antibodies Aother than@ the murine M195 antibody; principally chimeric M195 antibodies, humanized M195 antibodies, and conjugates of these antibodies.

Legal Principles: Support

Subsection 138(2) of the Patent Rules

[21] The Final Action cites subsection 138(2) of the *Patent Rules* as authority for the rejection for lack of support. That subsection states that AEvery claim must be fully supported by the description.@

[22] Canadian courts have provided little judicial interpretation of subsection 138(2) of the Rules or any of its equivalents. However in *Re Application of Ciba* (1974), Commissioner's Decision No. 208, the Board stated B after noting that it may be possible for a single sentence in the disclosure to provide sufficient support to warrant claims to some inventions B that the overriding principle was that an inventor may not validly claim what he has not described (citing *Radio Corporation of America v. Raytheon Manufacturing Co.* (1957), [1956-1960] Ex. C.R. 98 para 28, 27 C.P.R. 1 [*R.C.A.*]). The Board then went on to consider whether the invention had been sufficiently described as required by the statute [then Section 35 of the *Patent Act*; Subsection 27(3) for today=s purposes] and as expressed by the case law.

[23] This approach was also taken by the Board in a number of biotechnology decisions including: *Re Institut Pasteur Patent Application* (1995), 76 C.P.R. (3d) 206, Commissioner=s Decision No. 1206 when it considered whether there was specific Asupport@ for claims to monoclonal antibodies and hybridomas; *Re Application of Alonso* (2006), Commissioner=s Decision No. 1269 when the Board considered claims relating to monoclonal antibodies described through a deposit of a biological material; *Re Application of Yeda Research & Development Co.* (2007), 59 C.P.R. (4th) 464, Commissioner's Decision No. 1273 when the Board considered claims to nucleic acid molecules; and more recently in *Re Application of Central Sydney Area Health Service* (2008), Commissioner=s Decision No. 1283 when the Board again considered the question of specific support for monoclonal antibodies and nucleic acid molecules.

[24] Although compliance with subsection 138(2) of the *Patent Rules* may in some cases require little more than that the claims literally echo statements in the description, it can in other cases require more, and in our view an objection based on subsection 138(2) of the *Patent Rules* can be

substantive.

Subsection 27(3) of the Patent Act

[25] Since subsection 138(2) of the Rules is a subordinate form of legislation which cannot operate outside its enabling statute, and since the Board has previously considered the concept of Asupport@ in conjunction with subsection 27(3) (or its equivalent) of the Act, subsection 138(2) of the Rules should be read in conjunction with subsection 27(3) of the Act, which reads as follows:

> The specification of an invention must:
>
> (a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;
>
> (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 pertains, or with which it is most likely connected, to make, construct, compound or use it;
>
> (c) in the case of a machine, explain the principle of the machine and the best mode in which the inventor has contemplated the application of that principle; and
>
> (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.

[26] Compliance with paragraphs (a) and (b) of subsection 27(3) of the Act, and by extension subsection 138(2) of the Rules, requires respectively: (i) that the specification, beyond merely providing a generalized concept for an invention, provide a correct and full written description of the invention in meaningful terms; and separately, (ii) that the specification describe how of the invention actually was, or at least how it can be, put into practice: it must be enabling. In respect of each requirement it is understood that there must be correct and full compliance; AThe onus of disclosure that [subsection 27(3)] places on an inventor is a heavy and exacting one@: *R.C.A., supra.* Similarly, from the decision in *Farbwerke Hoechst A.G. vormals Meister Lucius & Bruning v. Canada (Commissioner of Patents)* (1965), [1966] Ex. C.R. 91, aff'd, [1966] S.C.R. 604 it is apparent that the claims must not exceed the invention made and that the claims must not exceed the invention which has been described in the specification.

[27] The decision in *Consolboard Inc. v. MacMillan Bloedel (Sask.) Ltd.*, [1981] S.C.R. 504 para. 22 - 23, 6 C.P.R. (2d) 146 makes clear the underlying reasons for requiring full compliance with subsection 27(3):

> Section 36 of the Patent Act [now subsection 27(3)] lies at the heart of the whole patent system. The description of the invention therein provided for is the *quid pro quo* for which the inventor is given a monopoly for a limited term of years on the invention.

[28] We appreciate that the specification need not exemplify and/or particularly describe every embodiment that may fall within the scope of the claims. Consideration is given to things which indicate that the applicant was in possession of the invention as claimed, such as the description

of relevant, specific, and meaningful identifying characteristics of the invention (e.g. structure, physical properties, chemical properties, functional characteristics, the provision of a representative number of embodiments, etc.). While actual physical construction of embodiments is not necessarily a strict requirement, it may be B particularly in the case of a biotechnological invention B that an invention cannot be correctly and fully described without having first obtained and then characterized a representative embodiment(s).

Analysis: Support for Antibodies

[29] The first part of the analysis will focus principally on the antibody molecules encompassed by claim 1. Any findings, whether favourable or not, in respect of this claim may be extended to other related follow-on aspects of the invention, including: therapeutic conjugates comprising antibodies; pharmaceutical compositions comprising antibodies; medical uses of antibodies; and Aantigen-binding fragments@ (which we take to mean $F(ab=)_2$ or Fab fragments wherein the Aarms@ of the antibodies are released through cleavage near the hinge region B see, for example, page 30, lines 16-24 of the description, which describes a well-known method of generating $F(ab=)_2$ fragments).

[30] The M195 antibody is a murine monoclonal antibody produced according to classical methods and it binds to a particular epitope found on the CD33 antigen. Claim 1 is directed to an antibody or antigen-binding fragment thereof, Aother than@ monoclonal antibody M195, which comprises an amino acid sequence capable of specifically binding to the epitope to which the M195 antibody binds. The term Aother than@ as used in claim 1 represents a negative limitation which finds no explicit basis in the specification as originally filed. That notwithstanding, claim 1 can be interpreted on its face as encompassing three types of antibody products which together compromise things Aother than@ the murine M195 monoclonal antibody itself, and which may all inherently carry Aan@ amino acid sequence capable of specifically binding to the same epitope to which monoclonal antibody M195 binds:

(i) other murine monoclonal antibodies which bind to the same epitope as the murine M195 monoclonal antibody;

(ii) chimeric, or hybrid, antibodies made up of the variable regions (as well as their attendant hypervariable regions or Acomplementary determining regions@- CDRs) of the murine M195 antibody attached to a human constant region; and

(iii) humanized antibodies which carry the same amino acid sequences of the hypervariable regions of the murine M195 antibody genetically engineered into a human variable region which itself is attached to a human constant region.

[31] The extent to which the specification provides adequate support for each of these types of antibodies will be considered in turn.

Support for Murine Monoclonal Antibodies AOther than@ the Murine M195 Antibody

[32] Claim 1 on its face can be interpreted as literally encompassing a murine monoclonal antibody that happens to bind to the same epitope as the M195 antibody. That claim 1 can be literally interpreted in this manner is not necessarily a reason to adopt this interpretation since the description goes no further and does not indicate that the invention is concerned in any way with

generating such Aother@ murine monoclonal antibodies.

[33] Therefore the specification fails to provide even literal written description of Aother@ murine monoclonal antibodies and the question of whether such antibodies are enabled need not be addressed.

[34] Although the description (see for example page 17, lines 1-11) indicates that the invention is generally concerned with Apolypeptides@ which carry the hypervariable region of the M195 antibody, after having dispensed with the possibility that the claims relate to Aother@ murine antibodies, we are led to the conclusion that claim 1 is, in effect, directed in the alternative to only two types of Aother@ things which we consider to be related yet distinct M195 follow-on products: chimeric M195 antibodies or humanized M195 antibodies. This assessment is consistent the teaching of the specification, the field of technology and the nature of the invention. For instance, the specification acknowledges the limitations of the murine M195 antibody in terms of its own potential to induce an undesirable human anti-mouse antibody immune response (HAMA) when used for leukemia therapy in humans and the M195 antibody=s limited ability to kill target cells through the use of cell complement or effector cells (see for example page 7, lines 9 to 26) in a human patient; hence the need and desire to generate chimeric or humanized forms of the M195 antibody.

[35] As stated above, we consider there to be a distinction between a chimeric M195 antibody and a humanized M195 antibody and we do not interpret the latter to be a subtype of the former.

Support for Chimeric M195 Antibodies

[36] Since the rejected claims on file at the time the Final Action was written did not relate to chimeric antibodies consisting of the M195 variable regions attached to a human constant region, the Final Action does not specifically address the question of whether the specification adequately describes and enables such antibodies. Instead it focuses more on humanized antibodies.

[37] The present application concerns monoclonal and genetically engineered antibodies directed against antigens carried by human cancer cells. The specification in our estimation is directed to a team of people including: a molecular immunologist with experience in monoclonal antibody production, immunoassays, and in cloning and expressing antibody genes; and a clinical oncologist specializing in leukemia therapies. The skilled person would not be expected to have specific knowledge of the CD33 antigen or of the murine M195 antibody.

[38] While it may have been feasible for the skilled person to construct a chimeric antibody through manipulations at the protein level, as suggested in both the Final Action and Applicant=s response, the present specification refers to a number of publications which all outline apparently more typical methods of generating chimeric antibodies through recombinant DNA techniques (see page 20, lines 9-15). In general these publications describe methods which involve the preparation of nucleic acid from cells that are known to produce a particular antibody (e.g. a murine hybridoma cell line) followed by screening or amplification techniques which are designed to yield DNA clones that encode the heavy and light chain variable regions. With these in hand it is then possible to generate expression constructs in which the cloned heavy and light chain DNAs are inserted in combination with segments encoding human constant regions. Expression in appropriate cells yields the desired chimeric antibody. A review article entitled *Production and Characterization of Genetically Engineered Antibody Molecules* (Morrison et

al., Clin. Chem., vol. 34, pp. 1668-1675, 1988 [*Morrison*]) nicely summarizes and explains the underlying biological principles as well as methods of generating chimeric antibodies. The article explains that the organization of the antibody heavy and light chain genes facilitates the isolation of the variable regions; that the exon structure of the antibody gene facilitates the joining of constant and variable regions; and perhaps more importantly, that variable regions can be readily cloned by using a J-region probe without any prior information as to the sequence of the variable region.

[39] It is therefore apparent that when cloning DNAs encoding the variable regions of an antibody B as distinct from the situation of cloning a DNA encoding other types of proteins of completely unknown structure B the skilled person would be able to take convenient advantage of the unique biology of immunoglobulin genes and what was known about them. Notably, the skilled person had knowledge, *a priori*, of DNA and amino acid sequence information of many constant regions as well as the general structures of framework regions within variable regions. Suitable probes and amplification primers (which are derived from known antibody nucleic acid sequences such as J segments and/or sequences from constant regions) were also known and it was known that these could be used to obtain virtually any variable region. Further, the skilled person knew that the cloning and rearranging of variable and constant regions from different species is facilitated by their genetic organization into discrete coding units (exons). While cloning and sequencing are techniques which often go hand-in-hand, we do not see that there is a need, strictly speaking, for a person of skill in the art to have obtained the complete nucleotide and/or amino acid sequence of heavy and light chain clones during the course of preparing a chimeric antibody; any sequencing done could have been limited and done simply for the purpose of verifying otherwise predicted cloning success.

[40] Having reviewed the relevant publications we are satisfied that, in general, methods of preparing chimeric antibodies were well known to a person of skill in the art and that such methods were reliable.

[41] In this particular case, the skilled person has been provided with a deposit of hybridoma cell line ATCC No. HB 10306, i.e., the source of genetic material for preparing DNA encoding the M195 light and heavy chain variable regions. A person of skill in the art need not be provided through the present specification with the other principle component of a chimeric M195 antibody gene since DNA constructs encoding human constant regions had previously been described, were well characterized and were previously available. With cell line HB 10306 in hand it would then be possible for the skilled person to follow the known methods mentioned in the specification, or otherwise known and available, for preparing heavy and light chain variable region clones, which could then be inserted into appropriate expression vectors in combination with human constant region segments. We note that two resultant chimeric mouse-human antibodies are described on page 147 and that the skilled person need not necessarily in all cases be informed of the particular details of how embodiments were constructed; chimeric M195 antibodies would be enabled if the steps involved in making them would be clearly apparent to the skilled person taking into account that person=s common general knowledge. The language used on page 147 indicates that chimeric antibodies Awere@ made and tested, and indicates, as a matter of fact, that generating functional chimeric M195 antibodies was actually possible. Further, page 147 states that cells making both chimeric antibodies grow well in culture, which is an indication that the chimeric antibodies were produced recombinantly in accordance with known chimeric antibody engineering techniques.

[42] To summarize the facts of this case, it is apparent that: the Applicant was actually in

possession of chimeric M195 antibodies; the basic methods for preparing chimeric antibodies were known; a source of genetic material suitable for cloning the M195 heavy and light chain variable regions was available; and there are no indications that a person of skill in the art would be unable to produce a chimeric M195 antibody. We therefore conclude that the present specification is enabling in respect of chimeric M195 antibodies.

[43] Concerning the requirement to provide a written description of chimeric M195 antibodies, we again note that, beyond a general or conceptual description of a chimeric M195 antibody, the present specification describes on page 147 two representative embodiments of chimeric M195 antibodies. These antibodies are further specifically described in terms of relevant characteristics including: the isotype of the human constant region; their binding affinities (described as similar to that of the murine M195 antibody); their method of production (by hybridoma cells which grow well in culture); and their ability to compete for binding with the M195 epitope.

[44] Although the present specification lacks a description of particular recombinant clones which express chimeric M195 antibodies and does not disclose the amino acid sequence of the M195 variable regions, we note that the Applicant neither claims recombinant clones nor does it appear that a claim to a chimeric antibody must necessarily in all cases rely on the recitation of amino acid sequences as a relevant identifying characteristic, especially, as is the case here, if representative embodiments have been provided and adequately described in other terms. Taking these facts into account we are satisfied that the present specification adequately describes chimeric M195 antibodies and that they may be claimed.

[45] Having found that the specification adequately describes and enables chimeric M195 antibodies, we consequently conclude that claim 1, insofar as it relates to such antibodies, is properly supported and therefore compliant with both subsection 138(2) of the *Patent Rules* and subsection 27(3) of the *Patent Act*.

[46] By extension this means that antigen-binding fragments of chimeric antibodies are also adequately described and enabled. However, to avoid any possibility that the term Aantigen-binding fragments@ of a chimeric antibody might be considered to encompass hypervariable regions, and for greater clarity and consistency with the teachings of the description, we propose to qualify the term to read AF(ab=)$_2$ or Fab antigen-binding fragments.@

Support for Humanized M195 Antibodies

[47] The following portions of the Final action outline, in part, the concerns with respect to humanized M195 antibodies:

> The preparation of humanized forms of M195 would require the isolation and manipulation of the DNA sequences encoding this antibody. No where has applicant demonstrated that they have isolated the sequences encoding M195 or provided any manipulated sequences. A DNA encoding a protein (including antibodies) is a completely separate chemical compound from the protein itself and constitutes a separate inventive concept.
>
> . . .
>
> It is well known in the art that all proteins must be encoded by a DNA sequence. However, the knowledge of the existence of this genetic information does not give an applicant the right to a patent on it. Only specific novel genetic information which has been isolated and characterized (ie sequenced) remains patentable. Applicant has not even demonstrated the preparation of an amino acid sequence for the M195 antibody

> let alone any genetic information for M195 that would be necessary for the preparation of humanized forms. Determination of amino acid sequences, preparation of DNA and then manipulating and expressing the DNA to prepare humanized forms of M195 would require undue experimentation on the part of one of skill in the art.
>
> . . .
>
> The applicant argues that one of skill in the art would know how to produce the humanized antibodies and conjugates and that the disclosure is enabling for their preparation because procedures for there preparation are referred to. The examiner concurs with the applicant on this point. However, the fact that one skilled in the art would know how to produce a useful substance (whether a procedure is novel or not) is not in itself support for the substance if it has not been disclosed. [emphasis in original]

[48] Based on the last paragraph in the above quotation it appears that the Examiner has presumed that the specification would have enabled the skilled person, based on their common general knowledge, to produce a humanized M195 antibody. On the other hand, the Final Action also states that the preparation and manipulation of DNA in order to prepare a humanized M195 antibody would require undue experimentation. We would say that, in general, knowing how to produce a claimed product and/or providing instruction in a specification as to how to go about producing a product does provide support for that product since such knowledge and instruction are indications that the specification is enabling. However, even if it appears that the skilled person may have been able to produce the product, it remains that a specification may not adequately describe that product.

[49] In response to the Final Action, the Applicant submitted, in part, the following:

> Applicant respectfully notes that genetic information is not being claimed, and the rationale for rejection is not germane to the actually claimed subject matter. Moreover, possession of the M195 antibody, and the antigen to which it binds, to clearly enables one of skill in the art to obtain without undue experimentation an antibody or antigen-binding fragment thereof, other than murine monoclonal antibody M195 (ATCC No. HB 10306), comprising an amino acid sequence capable of specifically binding to the epitope to which monoclonal antibody M195
> binds. With regard to this, applicant notes that is not a requirement for patentability under Canadian Law that a claimed product must have been made at the time of filing. The statement that, inter alia, determination of an amino acid sequence of the (obtained) M195 antibody would require Aundue experimentation@ is untenable. Amino acid sequencing and DNA preparation were facile and clearly routine to those of ordinary skill in the art at the time of filing.
>
> . . .
>
> Furthermore, humanized antibodies are well characterized by the specification, for example at page 20, line 23 to page 21, line 12. Humanized antibodies were well known in the art and humanized antibodies had been made and were found to maintain their antigen specificity. See, for example, Queen et al., AA Humanized Antibody that Binds to the Interleukin-2 Receptor@, Proc. Natl. Acad. Sci. USA, 86, pp. 10029-33 (1989) attached hereto as Exhibit C.
>
> Accordingly, applicant maintains that it would be of ordinary skill of the art to isolate the light chain and heavy chain proteins from an antibody directed to the antigen and then sequence those proteins using then-conventional and routine protein sequencing techniques. Applicant maintains that the various monoclonal antibodies claimed and the nucleic acids are well characterized in the specification and readily made without undue experimentation.

[50] In the response to the Final Action the Applicant has stated that A[h]umanized antibodies are

well characterized by the specification, for example at page 20, line 23 to page 21, line 12.@ These passages do not describe a humanized M195 antibody but do refer to several publications concerning other humanized antibodies and make it clear that several humanized antibodies which retain binding ability had been prepared and that techniques for preparing these antibodies had previously been described.

[51] In the response to the Final Action the Applicant also submitted a copy of an article (Queen et al., *A Human Antibody that Binds to the Interleukin 2 Receptor*, Proc. Natl. Acad. Sci. USA, vol. 86, pp. 10029-10033, 1989) in support of the contention that humanized antibodies were well known in the art. That article outlines a specific approach to making humanized antibodies and indicates that A[s]equence homology and molecular modelling [can be] used to select a combination of mouse and human sequence elements that would reduce immunogenicity while retaining high binding affinity.@ The article is neither cited in the specification nor are its teachings specifically described therein. However, the general strategy is somewhat reflected in the present specification on page 20, lines 23 to 30 and on page 146, lines 21 to 31. The article also indicates that simply transplanting murine amino acids from the hypervariable region into a human framework region may distort the conformation of the resultant humanized antibody thereby negatively affecting binding affinity. This suggests an element of unpredictability in the art. Consequently, the authors propose to identify additional key residues from the murine framework region for transplantation.

[52] After having studied the publications referred to in the specification and having considered the Applicant=s submissions, we surmise that very few laboratories were active in the field of antibody humanization and that only a limited number of antibodies had been successfully humanized (not thousands or even hundreds; more in the neighbourhood of ten). This indicates to us that the field, although not nascent, was still advancing as of the publication date of the application and that correctly identifying all the essential amino acids, both from the hypervariable region and the murine framework region, was important if the skilled person wanted to successfully generate a therapeutic humanized antibody.

[53] In this particular case, in order to enable a person of skill in the art to make or obtain a humanized M195 antibody it is necessary to first provide that person with a source of genetic material suitable for preparing DNA encoding the M195 light and heavy chain variable regions, i.e., a deposit of hybridoma cell line ATCC No. HB 10306. The following steps would then ensue:

- cloning of the variable region heavy and light chains;
- DNA sequencing of the same chains;
- aligning the sequences of the murine heavy and light chain genes with known human genes in order to identify the most homologous human gene;
- molecular modelling of the M195 variable regions in order to identify amino acids in the human framework regions which have significant contacts with the amino acids in the murine hypervariable regions;
- constructing overlapping oligonucleotides encoding newly designed heavy and light chain genes;
- inserting the genes into an appropriate vector;
- sequencing in order to verify that the desired heavy and light chain gene constructs had been made;
- expressing a humanized M195 antibody; and
- measuring affinity of the humanized antibody.

[54] It is understood that the making of a humanized antibody requires experimentation, but to what extent? The steps outlined above appear to be considerably more involved than would be the case for constructing a chimeric antibody.

[55] In this case no prototypical or working example of a humanized M195 antibody has been disclosed. This fact may not be determinative in itself but it is a fact which can work against a finding of enablement.

[56] Considering that the Applicant contemplates claiming variants (as indicated in the description on page 18, lines 11 - 15) of a prototypical humanized M195 antibody in which amino acids in the hypervariable region are changed, it is apparent that the design and construction of additional varied oligonucleotides would be required as would be the subsequent steps of sequencing, antibody expression and (hopefully successful) testing. This would amount to additional experimentation to be done without the benefit of any specific guidance and without the benefit of a prototypical humanized M195 antibody.

[57] The specification does not contain the sequence information of the murine M195 heavy and light chain variable regions. We understand that obtaining this information may be considered by the Applicant to be routine, but the sequence information is not part of the skilled person=s common general knowledge and it is information that is required to make a prototypical humanized M195 antibody and variants thereof.

[58] As outlined above, we have taken into account the nature of the invention, the maturity of the art, the knowledge and expectations of the skilled person, the amount of experimentation and effort required, the scope of the claims, the extent to which the Applicant has explored the claimed area, and the information and materials provided or disclosed in the specification. Taking these considerations into account we are not satisfied that the present specification would have enabled the skilled person to make a therapeutically useful humanized M195 antibody.

[59] Turning now to the question of written description, we understand that the Examiner, in apparent reference to this aspect and apart from considering the enablement aspect, maintains that there is a lack of support for the claimed humanized M195 antibodies themselves: A[t]he fact that one skilled in the art would know how to produce a useful substance or the fact that a disclosure teaches how to produce a useful substance (whether a procedure is novel or not) is not in itself support for the substance if it has not been disclosed.@

[60] In considering the requirement that a written description of a humanized M195 antibody be provided, we agree in part with the Applicant=s argument to the effect that Agenetic information is not being claimed@ and that the claims are not directed to DNA sequences that encode antibodies. Although it is true that protein molecules are encoded by DNA sequences we do not believe that it is necessary, as a general rule, for a claim to an antibody or a protein to be supported with a description of a complete DNA sequence which may encode it. Since the structures and amino acid sequences of human antibody constant regions and framework regions of variable regions were previously known, it does not seem necessary to provide the *complete* amino acid sequences of both heavy and light chains of a humanized M195 antibody in order to correctly and fully describe such an antibody.

[61] The antibodies of claim 1 are defined in terms of Aan amino acid sequence@ capable of specifically binding to Athe epitope@ to which the murine M195 antibody binds, yet the present

specification says nothing more specific in relation to the hypervariable regions of the murine M195 antibody or its cognate epitope. Though describing an amino acid sequence of a humanized M195 antibody as capable of binding to the epitope to which the murine M195 antibody binds does provide descriptive functional information for each of these binding partners, simultaneously referring to both partners, without further qualification, does not further illuminate the specific nature of either partner since such terminology merely restates in general functional terms what is obviously or inherently known B that a humanized M195 antibody must have the amino acid sequences of the hypervariable regions (derived from the murine M195 antibody), which would necessarily allow it to bind to some epitope on the CD33 antigen.

[62] While a specific description of the murine M195 epitope would provide relevant descriptive information of the murine M195 antibody, and by extension a humanized derivative thereof, a more meaningful description of a humanized M195 antibody can consist of a description of the amino acid sequences of the murine M195 antibody hypervariable regions. These amino acid sequences are relevant, specific and meaningful descriptors of a humanized M195 antibody, since it is these sequences which are transplanted into known human framework regions. Having said that, we do not discount the possibility that it may be possible to describe a humanized M195 antibody in other ways, for example by providing and characterizing actual embodiments.

[63] The instant specification provides neither a description of the hypervariable regions of the murine M195 antibody nor anything else that might relate specifically to a humanized M195 antibody. Accordingly, we find that humanized M195 antibodies are not adequately described.

[64] In summary we conclude that all claims related to humanized M195 antibodies are not compliant with both subsection 138(2) of the *Patent Rules* and with subsection 27(3) of the *Patent Act* since such antibodies are neither enabled nor adequately described. To be more certain, this finding is limited to the particular facts as they are in this case.

Analysis: Support for Conjugates

[65] Having found humanized antibodies to be neither enabled nor adequately described and therefore inadequately supported, it follows that conjugates of such antibodies are also problematic. However, since we have found that chimeric M195 antibodies are adequately supported, the question remains whether there is proper support for conjugates of these antibodies.

[66] The Final Action touches on the issue of support for antibody conjugates in relation to the prior art and it is also discussed as a formal objection under subsection 138(2) of the *Patent Rules*. The Final Action states, in part, the following:

> The only conjugate prepared in the instant application is a radionucleotide M195 conjugate which has already been disclosed in the prior art.
> . . .
> Applicant provides no support within the instant application for conjugates other than those which are old and known in the art (see arguments below).
> . . .
> Applicant has not prepared any conjugates other than to radionucleotides as discussed above . . .
>
> With regards to the preparation of conjugates, the examiner would point out that the applicant seems to be arguing two sides of the same argument. Applicant states that the

> *discussion* in the prior art of the preparation of conjugates, other than the radionucleotide conjugates disclosed, is insufficient support for the use of the art as a valid citation. However, the applicant's *discussion* of the preparation of potential conjugates without having prepared any, other than those already appearing in the prior art, should be considered sufficient support to claim these conjugates.
> Merely discussing the techniques which might be used does not provide support for the unprepared products. If applicant had actually prepared some toxin conjugates not found in the prior art, these might be considered patentable over and above any *discussion* of potential conjugates in the prior art. However, applicant has not prepared any novel conjugates.

[67] The Summary of Reasons maintains that the objection for lack of support for antibody conjugates applies in relation to the new claims submitted in response to the Final Action.

[68] The response to the Final Action does not specifically address the question of support for antibody conjugates since it focuses on the question of support for the claimed antibodies. However, a reply submitted by the Applicant on May 13, 2005 in response to an Office action issued November 13, 2004 does more specifically address this question. That reply stated, in part, the following:

> [A]pplicant has shown that monoclonal antibody M195, effectively carries agents conjugated to it into hematopoietic cells. ^{125}Iodine and ^{111}Indium conjugated to intact antibody M195 and the F(ab=)$_2$ fragment are internalized by HL60 myloid leukemia cells (see Experiment 3 at pages 74-85 of the description). Thus, applicant has shown to those skilled in the art that (1) the linkage between the M195 antibody and the conjugated agent is stable enough to not impede antigen binding; (2) this internalization allows the conjugate component to enter the cytosol; and (3) the linkage is stable enough to allow the conjugate to pass through other tissues.
> . . .
> The Examiner concedes that applicant has demonstrated preparation of M195 antibody-radionucleotide conjugates. Guidance for conjugating a toxin to those skilled in the art is supported, *inter alia*, on page 21, line 22 to page 22, line 16; on page 75, line 27 to page 76, line 5; and page 76, lines 20 to 33. The applicant has disclosed methods and prepared examples of conjugated antibodies with I^{125} and In^{111}. These examples provide guidance to those skilled in the art for the claimed conjugation embodiments. Conjugation technology was well known to those skilled in the art at the time this invention was made. Evidence that conjugation technology is well-known in the art can be found in disclosed references 57 to 63, in the production of commercial conjugated antibodies.
> . . .
> Applicant demonstrates effective use of the ^{131}I -M195 conjugates for treatments in their second Phase I clinical study disclosed on pages 105 and 106 of the description. The applicant describes the successful *in vivo* destruction of leukemia cells by the ^{131}I-M195 antibody.

[69] As the Applicant has pointed out, the successful preparation of several M195-toxin working embodiments (e.g. ^{125}I conjugates, as well as ^{111}In and ^{131}I radioimmune conjugates of M195 described at least in Experiments 3 and 4) has been demonstrated and the technology involved in their preparation was well known to a person of skill in the art. Further, there is nothing to suggest that a person of skill in the art would be unable to produce other M195-toxin conjugates. Concerning chimeric M195 antibody-toxin conjugates, we observe that the description on page 147 indicates that two chimeric antibodies which have been prepared retain, as expected, all of

the relevant characteristics of the original murine M195 antibody with the added benefit of having human constant regions. Since it does not appear that there is anything remarkable about the preparation of chimeric antibody conjugates, the skilled person would logically deduce that conjugates of a chimeric M195 antibody (which itself is adequately described and enabled) linked to known cytotoxins are adequately described and enabled, even if no such chimeric antibody conjugates have actually been physically prepared.

[70] Having reviewed the specification as well as the arguments presented by the Examiner and the Applicant, we are satisfied that conjugates of a chimeric M195 antibody are adequately described and enabled and therefore properly supported.

[71] This concludes our analysis of the first issue save for one minor point. We note that the Final Action raises a concern related to the issue of support: whether the claims rejected for lack of support under subsection 138(2) of the *Patent Rules* also fail to comply with paragraph 80(1)(f) of the *Patent Rules*. Paragraph 80(1)(f) of the *Patent Rules* concerns the requirement for the description to include examples, where appropriate, but applies only to applications filed on or after October 1, 1996. It is therefore not a proper grounds for rejection in the present case. Although the inclusion of examples in the description, even for applications filed on or after October 1, 1996, is not an absolute requirement, the presence, or not, of examples in the description is a valid consideration subsumed within the inquiry as to whether the specification is compliant with subsection 27(3) of the *Patent Act* and whether the claims are fully supported as required by subsection 138(2) of the *Patent Rules*. In the present case we have found that the absence of examples of humanized M195 antibodies militates against a finding of proper support whereas the absence of examples of chimeric M195 antibody-cytotoxin conjugates is not determinative in view of the fact that the specification describes actual chimeric M195 antibodies as well as the preparation and testing of prototypical murine antibody-cytotoxin conjugates.

ISSUE NO. 2: THE PRIOR ART

[72] The second main issue requires us to consider whether the claimed subject matter is anticipated or at least made obvious in view of two pieces of prior art cited in the Final Action. The prior art references are Tanimoto et. al. (Leukemia vol. 3(5), pp. 339-348, May 1989) and Scheinberg et. al. (Leukemia vol. 3(6), pp. 440-445, June 1989). Each of these references lists the inventor of the present application as an author and each reference is highly relevant in that each discusses the murine M195 antibody, its preparation, its binding specificity, its diagnostic utility, its potential as a therapeutic agent and so on. Indeed these articles parallel experiments 1 and 2 of the present specification.

[73] Claim 1 pending at the time the Final Action was written related specifically to a conjugate of the murine M195 antibody linked to a cytotoxic agent. This claim (as well as other related claims) was rejected for lack of novelty in view of Tanimoto or Scheinberg which each allegedly disclosed the same murine M195 antibody and conjugates thereof. In response to the Final Action claim 1 was cancelled and replaced with new claims which relate to antibodies (and conjugates thereof) Aother than@ the murine M195 antibody. In the Summary of Reasons the Examiner acknowledged that, in view of the exclusion of the M195 antibody, the claims could no longer be considered to be anticipated through prior disclosure of that antibody. Nonetheless, the Summary of Reasons indicated that another anti-CD33 antibody B which is termed MY9 and which allegedly has cross-blocking activity with the M195 antibody B fell within the scope of

new claim 1. The Summary of Reasons concluded with an indication that there is still nothing inventive in the application that has not already been anticipated Aor at least made obvious@ by the previous publications; indications which we take to mean that the Examiner still considers the prior art to be relevant. That being the case, and since the prior art was a serious point of contention, it is appropriate for the sake of completeness to consider whether the prior art anticipates or renders obvious the subject matter of the claims submitted in response to the Final Action.

Legal Principles: Anticipation and Obviousness

Anticipation

[74] Paragraph (a) of subsection 28.2(1) of the *Patent Act* relates to prior disclosures of inventions made by applicants (or by a person , such as an inventor, who obtained knowledge from the applicant) more than one year before the filing date of the application. That subsection was cited as authority for rejecting the claims for lack of novelty and it states the following:

> 28.2(1)
>
> The subject-matter defined by a claim in an application for a patent in Canada (the Apending application@) must not have been disclosed
>
> (a) more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant, in such a manner that the subject-matter became available to the public in Canada or elsewhere

[75] Subsequent to the Final Action, the Supreme Court handed down its decision in *Sanofi* and clarified that the test for anticipation has two aspects, disclosure and enablement, each of which must be addressed from the perspective of the skilled person in order to satisfy the test.

[76] Concerning the disclosure aspect, the Court indicated that the skilled person A[i]s simply reading the prior [art] for the purposes of understanding it@ and that at this stage A[t]here is no room for trial and error or experimentation by the skilled person@ (para. 25). If the disclosure requirement is met, the second requirement of enablement must also be satisfied; this means

A[t]hat the person skilled in the art would have been able to perform the invention@ (para. 26) and that A[t]he person skilled in the art is assumed to be willing to make trial and error experiments to get it to work@ (para. 27).

Obviousness

[77] Section 28.3 of the *Patent Act* prescribes that an invention must not be obvious and paragraph (a) is relevant to the present situation in the context of prior disclosures by inventors:

> 28.3
>
> The subject-matter defined by a claim in an application for a patent in Canada must be subject-matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to
>
> (a) information disclosed more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere

[78] In its decision the Supreme Court in *Sanofi* indicated at para. 67 that it will be useful in an obviousness inquiry to follow a four-step approach first outlined in *Windsurfing International Inc. v. Tabur Marine (Great Britain) Ltd.*, [1985] R.P.C. 59 (C.A.) and recently updated in *Pozzoli SpA v. BDMO SA*, [2007] F.S.R. 37, [2007] EWCA Civ 588.

[79] At the fourth step the Court further indicated that an Aobvious to try@ inquiry might be appropriate in areas of endeavour where advances are often won by experimentation (para. 68).

Analysis: Anticipation

Anticipation of New Claim 1

[80] In respect of new claim 1 submitted in response to the Final Action it is apparent that, through the use of the expression Aother than murine monoclonal antibody M195,@ the claim can no longer be considered to be anticipated since the murine M195 antibody has been excluded from the scope of the claim. Nonetheless, the Summary of Reasons provided to the Board draws our attention to the fact that the Final Action refers to another anti-CD33 monoclonal antibody, termed AMY9,@ which was commercially available more than one year before the filing date of the application and which was disclosed in both prior art references. The MY9

antibody was also discussed in an earlier examination report dated November 15, 2004. Although we have said that interpreting claim 1 to encompass Aother@ murine anti-CD33 antibodies, such as MY9, is an interpretation inconsistent and not supported by the remainder of the specification, we will nonetheless consider whether an apparently enabling disclosure of this Aother@ antibody might anticipate the new claim.

[81] According to the test for anticipation outlined in *Sanofi*, the disclosure requirement demands that the prior art reference disclose something which, if performed, would fall within the scope of the claim. Notwithstanding the fact that new claim 1 suggests that Aother@ anti-CD33 antibodies, such as the MY9 antibody, are encompassed within its scope, it is apparent that the claim is also limited to those antibodies which are Acapable of specifically binding to the epitope to which monoclonal antibody M195 binds@ and that claim 1 does not more broadly encompass antibodies that are capable of binding to the CD33 antigen in a manner competitive with the murine M195 antibody.

[82] In comparing the binding properties of M195 and MY9, the Scheinberg reference reports that there is cross-blocking activity between the two antibodies (see page 442, left-hand column, last paragraph bridging to the right-hand column), a finding which indicates that the two antibodies bind to the same CD33 antigen. However, flow cytometry data indicated that there were non-identical immunoreactivity patterns between the two (see table 5). The paper concludes (on page 444, left-hand column, second paragraph) that:

> Blocking experiments shown here demonstrate probable identity of the M195 target with the CD33 protein. . . . Despite these data, since flow cytometry data showed nonidentical concordance with MY9, it is likely that M195 does not bind to the same CD33 epitope as MY9 or L4F3.@[emphasis added]

[83] From this we conclude that the prior art MY9 antibody (or even the other AL4F3@ antibody mentioned in Scheinberg or Tanimoto) does not fall within the scope of new claim 1 since it has not been established that it is Acapable of specifically binding to the epitope to which monoclonal antibody M195 binds.@

[84] Although we could conclude on that basis alone that new claim 1 is not anticipated by either reference, we would further note that there are other differences between the subject matter of other claims on file and the prior art. For instance, concerning claims related to conjugates, we note that neither reference discloses a cytotoxic agent linked to either the MY9 antibody or the L4F3 antibody.

[85] Most importantly, to the extent that new claim 1 (and related claims) relates to a chimeric or humanized M195 antibody, we note that neither prior art reference discloses either a chimeric or humanized M195 antibody, let alone a conjugate thereof. Therefore chimeric and humanized M195 antibodies are not anticipated by either reference.

[86] At the time the Final Action was written the question of whether the prior art enables the critical starting material for the production of chimeric antibodies and humanized M195 antibodies (i.e. the hybridoma which produces the murine M195 antibody) was a major point of contention. The question of enablement of the M195 antibody is also something that may factor into an obviousness analysis. We therefore consider it necessary and appropriate in this case to also address the question of whether the prior art satisfies the enablement aspect of the test for anticipation.

Anticipation and the Question of Enablement

[87] If a prior art reference is not enabling in respect of a starting material, and if that material cannot be otherwise obtained, it follows that derivative products are also not enabled by the same prior art reference. Since the starting material for the creation of a chimeric or humanized M195 antibody is the hybridoma cell line that produces the murine M195 antibody, the question of enablement of the hybridoma and the M195 antibody itself is therefore a highly relevant consideration in the present case.

[88] The Final Action cited the articles by Scheinberg and Tanimoto against the rejected claims and indicated that each publication, on its own, is anticipatory:

> References Re-Applied:
>
> Tanimoto, M., et. al. Leukemia 3(5):339-348 (May 1989)
> Scheinberg, D.A., et. al. Leukemia 3(6):440-445 (June 1989)
>
> Tanimoto, et. al., disclose the preparation of the M195 antibody. Methods for obtaining the antibody are clearly and fully disclosed. Tanimoto, et. al., further disclose the preparation of ^{125}I-labelled purified M195 and F(ab)'2 fragments of M195 (see page 341, second column). Tanimoto, et. al., further state that the antigen detected by M 195 A...is not detectable on any other adult tissues and thus may be useful in the study of myelomonocytic differentiation and in the diagnosis and therapy of ANLL.@ Experiments within the paper demonstrate the antibody's biological activity, including the fact that the antibody is rapidly internalized.
>
> Scheinberg, et. al., also disclose the monoclonal antibody M195 and its further characterization as a tool for diagnosis and treatment of ANLL. Scheinberg, et. al., disclose that together with another antibody MY9, M195 showed 98% specificity in diagnosing ANLL in clincal samples. Like Tanimoto, et. al., Scheinberg, et. al., disclose radio-labelled M195. Scheinberg, et. al., also demonstrate that M195 could be used as a purging agent in ANLL and discusses the use of M195 as a therapeutic agent in vivo. Based on the rapid internalization of M195 it is stated that M195 would be a good carrier for toxins or isotopes to ANLL cells.
>
> The examiner has identified the following defects in the application:
>
> Claims 1, 3 to 13, 15 and 18 to 31 are found not to comply with Paragraph 28.2(l)(a) of the Patent Act in view of Tanimoto, et. al. and Scheinberg, et. al., cited above. Tanimoto, et. al. and Scheinberg, et. al., both disclose and characterize the M195 antibody of the instant application. In their arguments of May 13, 2005 Applicant reasserts their position that without a deposit the antibody M195 has not been made available to the public. The inclusion of deposit numbers and sequences are not requirements in Canadian practice for the full disclosure of a monoclonal antibody. In fact a deposit number on its own does not constitute sufficient disclosure but rather provides further characterization of an antibody. Applicant is referred to the Manual of Patent Office Practice (MOPOP), Section 17.03 which states: AReference to a deposit is not intended to replace a written description of an invention but rather to supplement it.@ By disclosing the antibody M195, which applicant admits is the same antibody as that disclosed in the instant application, along with the methods for its preparation, applicant has made the Asubject-matter@of the claims available to the Canadian public more than one year prior to the filing of the instant application (Subsection 28.2(l) of the Canadian Patent Act reads: AThe subject-matter defined by a claim in an

> application for a patent in Canada (the Apending application@) must not have been disclosed ...@). A published application which describes how to build a widget, and successfully prepares the widget, has disclosed that widget even though none have ever been sold to the public. The addition of a deposit number to the characterization of M195 in the instant application does not therefore constitute enabling disclosure on its own, but rather further characterization of an already disclosed antibody. The Tanimoto and Scheinberg references disclose the M195 antibody by name as well as all of the techniques necessary to prepare this antibody. For purposes of patenting in Canada this would be considered full and complete disclosure of this antibody. Applicant is not therefore entitled to claim an antibody which they have previously disclosed.
>
> . . .
>
> Also, as discussed above, the examiner finds that the prior art provides full and complete disclosure not only of M195 but also of conjugates of this antibody to various radioisotopes which can be considered, and are indeed used by the applicant, as toxins. Applicant provides no support within the instant application for conjugates other than those which are old and known in the art (see arguments below).

[89] The arguments made in the Final Action to the effect that the murine M195 antibody and conjugates thereof were fully and completely disclosed more than one before the filing date were not completely addressed by the Applicant in the response to the Final Action. Rather, claim 1 was cancelled and the Applicant indicated, in relation to the replacement claim, that A[t]he cited references do not teach a monoclonal antibody, other than murine monoclonal antibody M195 (ATCC No. HB 10306), comprising an amino acid sequence capable of specifically binding to the epitope to which monoclonal antibody M195 binds.@ In order to fully appreciate the Applicant=s perspective on the question it is therefore necessary to consider the Applicant=s earlier response of May 13, 2005 (briefly mentioned in the Final Action); that earlier response states, in part, the following:

> (i) <u>The M195 Antibody was not publicly available to the Canadian public prior to the filing date of this application.</u>
>
> The Examiner alleges that the antibody M195 was available to the Canadian public prior to the filing of this application.
>
> Applicant respectfully disagrees, and notes that the Examiner has failed to address applicant's previously submitted copy of a declaration of Dr. David A. Scheinberg, who is the inventor of the subject matter claimed in the present application. A copy of this declaration is again attached hereto as Exhibit A for the Examiner's convenience.
>
> In the declaration, Dr. Scheinberg declares that he is a co-author of both the Tanimoto et al. and Scheinberg et al. references. Dr. Scheinberg further declares that before December 14, 1989, the priority date of the present application, monoclonal antibody M195 and the corresponding hybridoma cell line were not publicly available, and further that they were distributed, if at all, with the understanding that they were to be maintained in confidentiality. The Declaration was originally submitted in connection with related European application No. 91 904912.2, now European Patent No. 0504327.
>
> In addition, applicant submits a copy of a declaration from Lloyd J. Old, the supervisor of the inventor and custodian of the M195 antibody at the time of the invention. A copy of this declaration is again attached hereto as Exhibit B for the Examiner's convenience. In the declaration, Dr. Old declares that before December 14, 1989, the

> priority date of the present application, the M195 antibody was not publicly available. The Declaration was originally submitted in connection with related International Application No. PCT/US90/07436, now U.S. Patent No. 6,007,814.
>
> . . .
>
> (ii) Tanimoto and Scheinberg do not Teach the M195 Antibody in an Enabling Disclosure.
>
> Applicant respectfully submits that one skilled in the art cannot practice the invention of the M195 antibody by simply following the disclosure of Tanimoto et al. or Scheinberg et al. without undue experimentation. Neither of these references provides an enabling disclosure of monoclonal antibody M195. For this reason, neither reference makes the subject invention available to the Canadian public. Applicant again points out that neither Tanimoto et al. nor Scheinberg et al. describes a specific method for preparing or isolating the M195 antibody. Tanimoto and Scheinberg describe a general screening procedure that isolates monoclonal antibodies reactive with cells. This procedure involves screening several hundred hybridoma-produced antibodies and isolating the M195 antibody.
>
> . . .
>
> In addition, applicant respectfully disagrees with the Examiner's assertion that a deposit is not necessary to practice the invention of the M195 antibody. The Examiner cites MOPOP '17.03 as stating that a AReference to a deposit is not intended to replace a written description of an invention but rather to supplement it.@ However, MOPOP '17.03 also states that Awhen an invention is a biological material or when a biological material is needed to practice an invention, *words alone may not be sufficient* to fulfill the statutory obligations of subsection 27(3) of the Patent Act.@(Emphasis added.) Absent a deposit, those skilled in the art could not obtain the M195 antibody without re-screening, and re-isolating it from, hundreds of hybridomas producing hundreds of antibodies. The Examiner has not established a guarantee or even a likelihood of success in re-isolating the M195 antibody simply by following the procedure described in Tanimoto or Scheinberg.

[90] From the Applicant=s response we take it that it is undisputed that either the Tanimoto or the Scheinberg reference disclosed the murine M195 antibody mentioned in the claim more than one year before the filing date of the present application. Therefore, at the time the Final Action was written the question of anticipation appears to have been centred on the enablement aspect of the test and, in particular, whether a person of skill in the art, although understanding that each reference disclosed the M195 antibody and conjugates thereof, would have been able to perform the claimed invention by making trial and error experiments.

[91] Concerning the enablement aspect of the test for anticipation, the Supreme Court in *Sanofi* offered a non-exhaustive list of factors (at para 37) which should normally be considered:

> 1. Enablement is to be assessed having regard to the prior patent as a whole including the specification and the claims. There is no reason to limit what the skilled person may consider in the prior patent in order to discover how to perform or make the invention of the subsequent patent. The entire prior patent constitutes prior art.
>
> 2. The skilled person may use his or her common general knowledge to supplement information contained in the prior patent. Common general knowledge means knowledge generally known by persons skilled in the relevant art at the relevant time.
>
> 3. The prior patent must provide enough information to allow the subsequently

> claimed invention to be performed without undue burden. When considering whether there is undue burden, the nature of the invention must be taken into account. For example, if the invention takes place in a field of technology in which trials and experiments are generally carried out, the threshold for undue burden will tend to be higher than in circumstances in which less effort is normal. If inventive steps are required, the prior art will not be considered as enabling. However, routine trials are acceptable and would not be considered undue burden. But experiments or trials and errors are not to be prolonged even in fields of technology in which trials and experiments are generally carried out. No time limits on exercises of energy can be laid down; however, prolonged or arduous trial and error would not be considered routine.
>
> 4. Obvious errors or omissions in the prior patent will not prevent enablement if reasonable skill and knowledge in the art could readily correct the error or find what was omitted.

[92] Concerning the first factor, although in the present case neither piece of prior art is a prior patent, it is understood that the whole of each article may be independently considered and we have done so.

[93] Concerning the second factor, we are satisfied that the skilled person, being familiar and experienced in the well-known techniques of murine monoclonal antibody production as well as the preparation of conjugates, would have been able to safely rely on his common general knowledge to supplement the technical instructions provided in either Scheinberg or Tanimoto if that person were to attempt to reproduce the M195 antibody. That same common general knowledge, in respect of the fourth factor, could be relied upon to readily correct any errors or omissions in the M195 preparation protocol which is best described in the Tanimoto reference.

[94] This leaves the third factor to consider.

[95] After the Final Action was written chapter 17 of the *Manual of Patent Office Practice*, which concerns biotechnology practice, was updated. We note that subsection 17.04.02, under the main heading ASufficiency of description,@ states, in relation to deposited biological materials, the following:

> Where the invention cannot be enabled [see 17.04] in the absence of access to a biological material, however, the deposit is a necessary element to make the description sufficient unless the required material is publicly known and reliably available to the person skilled in the art. A biological material is considered to be reliably available if it can be obtained commercially or can be reproducibly prepared or isolated from available materials using established procedures and without undue experimentation.

[96] Subsection 17.05.01, under the main heading ANovelty,@ similarly states the following:

> Recall from 17.04.02 that a description may be considered not to be sufficient unless it provides access, via a deposit made as of the filing date, to biological material associated with the invention. This requirement extends to an allegedly anticipatory disclosure.
>
> Consequently, if the disclosure found in the prior art requires, in order for the invention described therein to be practised, access to a biological material, the biological material must necessarily have been reliably available to the person skilled in the art in order for the document to be anticipatory. To be reliably available it must be either

> commercially available, be reproducibly preparable or isolable from available materials using established procedures and without undue experimentation, or be accessible via a deposit of biological material.

[97] We also take note of decision T 0576/91 of the European Patent Office=s Boards of Appeal which, although not binding, is informative. In addressing the question of whether a prior art reference disclosing a particular biological material anticipated a claim directed to the same biological material, the board found that the reference was not Aintrinsically@ enabling and, in so finding, stated the following:

> It is generally recognised that the aim of a scientific publication is to inform the public in writing about a teaching or a discovery which has been made. In the scientific community the free exchange not only of technical information, but also of biological material is generally encouraged.
> . . .
> Despite the fact that this unwritten rule appears to be generally accepted within the scientific community, the Board is unable to conclude that it amounts to an obligation, so that any biological material which is the subject of a publication can in effect be considered publicly available.

[98] Thus the mere disclosure in a scientific article of an antibody or hybridoma cell line does not necessarily mean that the antibody and/or cell line would have been available to the public in an unrestricted manner as of the publication date of the article.

[99] In the present case it is apparent that the hybridoma cell line producing the M195 antibody was neither commercially available nor had it been made publically available in a biological material depository more than one year before the filing date of the present application. This has been established through the provision of exhibits A, B and C which accompanied the Applicant=s response of May 13, 2005 and which were also submitted in other jurisdictions during the prosecution of the equivalent foreign applications. Exhibit A is a declaration from inventor Scheinberg which states that the M195 antibody and its corresponding hybridoma were not freely available to the public before December 14, 1989. Exhibit B is a corroborating declaration from Scheinberg=s supervisor. Exhibit C is a copy of the acknowledgement letter dated December 14, 1989 from the American Type Culture Collection for the deposit of hybridoma cell line HB 10306. Based on the record before us, we have no reason to doubt the veracity of these documents. While a bald assertion that the hybridoma cell line was not freely available to the public may not suffice to establish non-availability, the provision of supporting documentation, as is the case here, establishes this to our satisfaction.

[100] Since the M195 antibody or its corresponding hybridoma was neither commercially available nor available from a depository, we are left to consider whether the M195 antibody could have been prepared independently from available materials using the disclosures of either Scheinberg or Tanimoto, without undue experimentation.

[101] It should be borne in mind, and it cannot be overemphasized, that the claims of the present application are narrow and refer to a particular monoclonal antibody produced by a particular deposited hybridoma cell line. The first task faced by the skilled person in this case is to *independently* reproduce *the* M195 murine antibody produced by hybridoma cell line ATCC HB 10306 and *not* one which is merely similar to it. The M195 antibody has a number of unique features which distinguish it from other anti-CD33 antibodies; for instance, it targets a particular epitope carried by the CD33 antigen, it is of a certain isotype, it binds with high affinity to its

target, it inherently has unique hypervariable regions, and it is rapidly internalized into cells after binding.

[102] According to the third factor mentioned in *Sanofi*, AWhen considering whether there is undue burden, the nature of the invention must be taken into account.@ In this case, although it may be reasonable to say that the steps themselves involved in reproducing the M195 antibody are routine, it is arguable that, because of the nature of the invention, the reproduction of the M195 antibody entails more than routine trial and error experiments and instead involves good luck or at least something more prolonged and arduous than routine trial and error experiments.

[103] The skilled person would know that antibody diversity in mammalian immune systems is vast. Mammalian immune systems typically react to exposure to a foreign polypeptide immunogen by generating an array of antibodies that bind with varying affinities to a variety of epitopes carried by the immunogen B the more complex the immunogen, the greater the diversity of the immune response. These antibodies also vary in type, subtype, and each antibody-producing B cell produces an antibody with its own inherently unique hypervariable regions. Although not inconceivable, generally speaking the skilled person recognizes that it is unlikely that independently derived monoclonal antibodies with the same general polypeptide specificity will have identical properties.

[104] Considering the specifics of the present case, it is apparent that the immunogen which would be used to reproduce the M195 antibody is CD33 B a glycoprotein antigen 67 KDa in size carrying numerous possible epitopes. It is further apparent that each prior art reference discloses three different types of anti-CD33 monoclonal antibodies (the M195 antibody as well as other antibodies termed AMY9@ and AL4F3@) which bind to different epitopes on CD33; a fact which confirms that providing the same CD33 antigen can result in the independent production of anti-CD33 monoclonal antibodies with differing properties and structures.

[105] We are therefore not satisfied, at least based on the record in this case, that a person of skill in the art would have been able to independently arrive at the same M195 antibody referred to in the claims, and thereby enable the claimed invention, without being asked to engage in hopeful yet prolonged and arduous experimentation. Since the present case is somewhat unique, we should not be taken to say that a scientific article describing a product can never be a valid citation for the purposes of anticipation unless it also provides a deposit of a biological material for producing the product; to the contrary, enablement of products previously disclosed is normally presumed.

[106] Since neither prior art reference would enable a person of skill in the art to reproduce or otherwise obtain the M195 antibody, the chimeric and humanized antibodies of claim 1 (and related claims) cannot be considered to be anticipated even if they had been previously disclosed.

Analysis: Obviousness

[107] Although the subject matter of claim 1 (and related claims) has been found to be novel, it has been suggested in the Summary of Reasons that A[w]hile applicant has amended some of the claims in its response to the final action, there is still nothing inventive presented in this application that has not already been anticipated or at least made obvious by the applicant's

previous publications@[emphasis added].

[108] We will therefore proceed with an obviousness analysis to address any lingering concerns that the claims are obvious in view of the cited references. Since this was not a point of contention at the time the Final Action was written and only arose in light of the newly submitted claims, the Applicant was given the opportunity in a letter from the Board to address the question of obviousness in light of the approach subsequently presented in *Sanofi*. However, the Applicant chose not to make any submissions.

[109] The four-step approach outlined in *Sanofi* entails the following:

> (1) (a) Identify the notional Aperson skilled in the art@;
>
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the Astate of the art@ and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[110] We apply this approach to the present case in the following manner.

Identify the notional Aperson skilled in the art@

[111] The specification in our estimation is directed to a team of people including: a molecular immunologist with experience in monoclonal antibody production, immunoassays, and in cloning and expressing antibody genes; and a clinical oncologist specializing in leukemia therapies.

Identify the relevant common general knowledge of that person

[112] The skilled person would have knowledge of cell surface markers and antibodies directed thereto but not necessarily the CD33 antigen or anti-CD33 antibodies; techniques which could be used to make chimeric or humanized versions of murine monoclonal antibodies; and would know that monoclonal antibodies, chimeric antibodies and humanized antibodies directed to leukemia cell surface markers could be conjugated with cytotoxic agents and that such conjugates represented potential leukemia therapeutics.

[113] That immunoconjugates had potential therapeutic application in treating leukemia is supported by the description, wherein we note on page 4 at lines 23 to 27 that, according to the seven cited references, there apparently had been several clinical trials in which radiolabeled monoclonal antibodies were investigated for their potential in treating lymphomas and leukemia. Our more general assessment of the common general knowledge is supported by reference to a book entitled *Therapeutic Monoclonal Antibodies*, Borrebaeck and Larrick, eds. (New York: Stockton Press, 1990 [*Borrebaeck*]). Although they showed promise, we are not convinced that therapeutic immunoconjugates had been widely approved for leukemia treatment or had become

commonplace in medical practice in late 1989. This is acknowledged, for example, in the preface of *Borrebaeck* wherein the editors state that:

> Despite the relative ease of producing murine antibodies, the original promise of Mab technology for the generation of novel therapeutic molecules is just now being recognized. This late acknowledgement has mainly been caused by technology-related problems with the generation of human Mabs and with the selection of targets for mouse Mabs.

[114] Further, in chapter three of *Borrebaeck* authors Bator and Reading reported at page 35 that AIn recent years, clinical trials using such conjugates have been undertaken but again have met with mixed success.@

Identify the inventive concept of the claim in question or if that cannot readily be done, construe it

[115] The inventive concept expressed in claim 1 is a murine M195-derived chimeric or humanized antibody that can be used for treating leukemia. If not entirely discernible from the claim on its face, the intended therapeutic application of the antibody is implicit and is further evident from the description as well as the other claims on file which exclusively refer to therapeutic agents and conjugates. Based on the description we further understand that this inventive concept stems from the realization that the M195 antibody does indeed possess therapeutic potential. We do not accept that the inventive concept expressed in claim 1 can be related to another type of anti-CD33 antibody, such as the MY9 antibody, since the claim is specifically related to the M195 antibody and its specific cognate epitope.

Identify what, if any, differences exist between the matter cited as forming part of the Astate of the art@ and the inventive concept of the claim or the claim as construed

[116] For our purposes, the two prior art references will be considered as a whole since there is a clear link between the two (each references the other as a relevant document).

[117] The prior art indicates that Ait may be feasible@ to use the M195 antibody as a carrier of cytotoxins to treat leukemia (see for example, the Scheinberg reference at page 444, right-hand column last sentence) but does not provide any clincal data to support that assertion; instead the article outlines immunoassays which indicate that the antibody has an appropriate pattern of reactivity. It is further apparent that neither reference discloses a therapeutic radioimmune conjugate; instead each discloses conjugates used for cross-blocking studies.

[118] It is also apparent that, based on the foregoing anticipation analysis, neither reference would have enabled a person of skill in the art to reproduce or otherwise obtain the M195 antibody and that neither reference discloses a chimeric or humanized M195 antibody.

Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[119] In *Sanofi*, the Supreme Court indicated that this fourth critical question can be addressed by considering whether the invention was Aobvious to try.@ Such a test may be appropriate in Aareas of endeavour where advances are often won by experimentation@(para 68). We consider

the nature of the invention in the present case warrants such a test.

[120] If an obvious to try test is warranted, the Supreme Court indicated that the following factors should be taken into consideration at the fourth step of the obviousness inquiry (at para. 69):

> (1) Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?
>
> (2) What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
>
> (3) Is there a motive provided in the prior art to find the solution the patent addresses?

[121] Considering the first factor, it would have been apparent to the skilled person, based on what was commonly known and what was disclosed in the cited references, that anti-CD33 antibodies, such as the M195 antibody, were attractive compounds warranting further investigation. However, it is somewhat difficult to say whether or not it was more or less self-evident that trying either a chimeric or humanized version of the M195 antibody ought to work as a leukemia therapeutic in patients. As we have said, it does not appear that leukemia therapies using antibody constructs had been put into widespread use at the time. Although it appears that a possible solution had been identified and may have been Aworth a try@, we are not well enough satisfied that that possible solution rises to the level of being one which would have been predictable by a person of skill in the art so as to be Aobvious to try.@

[122] Concerning the second factor, it is apparent that the starting point in order to achieve the invention outlined in claim 1 is the M195 antibody. The hybridoma producing the M195 antibody would be required in order to generate chimeric and humanized M195 antibodies. In the anticipation analysis we have concluded that it has not been established that the M195 antibody and its hybridoma could have been obtained without engaging in prolonged or arduous work. It therefore appears that even getting to the starting point of the invention would have been a challenge. We note that when it considered the second factor in the obvious to try inquiry the Supreme Court in *Sanofi* alluded to a connection between enablement in the context of anticipation and the second factor in the context of obviousness. Although the second factor assumed smaller significance in that case the Court stated (at para. 89):

> As in the case of anticipation, one might infer that the applications judge, if asked to decide this question, would have held that the investigation here was not routine, but rather was prolonged and arduous.

[123] We are mindful that there may be a distinction between the concept of enablement in the context of anticipation and the requirement that the skilled person, in an obviousness inquiry, not be called upon to engage in prolonged and arduous experimentation. In the present case, similar to the case in *Sanofi*, we draw a negative inference from our findings on enablement in the context of anticipation and borrow it for the purposes of our obviousness analysis. We observe that the prior art, although being closely related to the claimed subject matter, represents an artificial starting point, which, even if reached by the skilled person, would still be at least some distance away from the invention as it is claimed.

[124] Considering the third factor, we observe that the conclusion on the second factor can be seen as an obstacle to the skilled person. A person of skill in the art, although arguably possessed with

sufficient motivation in general to find a solution to the treatment of leukemia, if faced with the prospect of having to first engage in prolonged experimentation in order to generate the M195 starting material, would not be overly motivated to try to produce that specific starting material as a first step. The question also arises whether the skilled person would have been more likely to pursue experiments involving the use of other similar antibodies (albeit perhaps not quite as good), such as MY9, which were readily available and which also represented alternative avenues of investigation.

[125] The actual course of conduct which culminated in the making of the invention is also a valid consideration in an obviousness inquiry (*Sanofi* para 70). In the present case, it is evident that there is a time gap between the time of filing and the publication dates of the prior art: the prior art dates to May-June 1989 whereas the present application was filed in December 1990 B a gap of eighteen months. It is further evident that the present specification contains considerably more information than does the combination of the prior art references. Although Experiments 1 and 2 of the present specification correspond to the Tanimoto and Scheinberg references respectively, the present specification goes considerably further, in terms of describing the therapeutic potential of the M195 antibody and conjugates thereof, than does the prior art. For instance the present specification discloses additional *in vivo* experiments and phase I clinical trials in patients (see notably experiments 3, 4, 5, 6 and 8). The specification favourably reports and includes data on things such as antibody internalization into cells, radionuclide release into tumour cells, M195 toxicity, and pharmacologic profile. Contrary to what is stated in the Final Action to the effect that the only conjugate prepared in the instant application is a radionucleotide M195 conjugate which has already been disclosed in the prior art, we again note that the present specification does indeed disclose other radionucleotide conjugates, such ^{111}In and ^{131}I radioimmune conjugates of M195 described at least in Experiments 3 and 4. Furthermore, the specification reports on page 106, first paragraph in relation to the phase I clinical study, that Aenormous cell killed [sic] was demonstrated in 6 of 8 patients@ and that there was no significant non-hematologic toxicity. This indicates to us that additional work and experimentation was conducted in the course of developing the invention ultimately claimed in the present application.

[126] Taking into account these considerations we have come to the conclusion that the invention expressed in claim 1 (and related claims) in respect of chimeric and humanized M195 antibodies would not have been obvious to try and consequently find it nonobvious. This finding can be extended to the remaining claims on file since they more specifically relate to humanized M195 antibodies or therapeutic conjugates.

SUMMARY

[127] The new claims are neither anticipated under paragraph 28.2(1)(a) of the Act by either of the cited references nor are they obvious under paragraph (a) of section 28.3 of the Act in view of the combination of the same references.

[128] We have found new claim 1, insofar as it relates to humanized M195 antibodies and Aother@ murine antibodies, to lack support within the meaning of subsection 138(2) of the *Patent Rules* and not to be in compliance with subsection 27(3) of the *Patent Act*.

[129] New claim 1, insofar as it relates to chimeric M195 antibodies, is compliant with both subsection 138(2) of the Rules and subsection 27(3) of the Act. By extension this also applies to Aantigen-binding fragments@ of a chimeric antibody (which for greater certainty should read

AF(ab=)$_2$ or Fab antigen-binding fragments@ as explained in paragraphs 29 and 46). This means that claim 1 must be restricted to a chimeric monoclonal antibody, or an F(ab=)$_2$ or Fab antigen-binding fragment thereof, wherein said chimeric monoclonal antibody comprises the variable regions of antibody M195 (ATCC HB 10306) and a human constant region.

[130] Finally, we note that paragraph 80(1)(f) of the Rules is not applicable in the present case.

RECOMMENDATION AND RULE 31(C) AMENDMENTS

[131] In accordance with paragraph 31(c) of the *Patent Rules*, it is our recommendation that the Commissioner inform the Applicant that the following amendments are necessary for compliance with the Act and Rules:

(1) restriction of claim 1 to a chimeric monoclonal antibody, or an F(ab=)$_2$ or Fab antigen-binding fragment thereof, wherein said chimeric monoclonal antibody comprises the variable regions of antibody M195 (ATCC HB 10306) and a human constant region,

(2) deletion of claims 2 through 6 and 20 through 42; and

(3) adjustment of all claim numbering and dependencies accordingly.

[132] We further recommend that:

(i) the Applicant be invited to make only the above amendments within three months from the date of the Commissioner=s decision;

(ii) the Applicant be advised that, if the above amendments and only the above amendments, are not made within the specified time, the Commissioner intends to refuse the application; and

(iii) the Applicant be advised that, if the above amendments and only the above amendments, are made within the specified time, the Commissioner will consider the outstanding issues to have been addressed.

Ed MacLaurin	Paul Fitzner	Nicole Harris
Member	Member	Member

COMMISSIONER=S DECISION

[133] I concur with the findings and recommendation of the Patent Appeal Board.

[134] In accordance with paragraph 31(c) of the *Patent Rules*, I hereby inform the Applicant that the following amendments are necessary for compliance with the Act and Rules:

(1) restriction of claim 1 to a chimeric monoclonal antibody, or an F(ab=)2 or Fab antigen-binding fragment thereof, wherein said chimeric monoclonal antibody comprises the variable regions of antibody M195 (ATCC HB 10306) and a human constant region,

(2) deletion of claims 2 through 6 and 20 through 42; and

(3) adjustment of all claim numbering and dependencies accordingly.

[135] I invite the Applicant to make the above amendments, and only the above amendments, within three months from the date of this decision, failing which I intend to refuse the application.

[136] If the above amendments, and only the above amendments, are made within three months from the date of this decision I will consider the outstanding issues to have been addressed.

Mary Carman

Commissioner of Patents

Dated at Gatineau, Quebec
this 5th day of November, 2009