Commissioner's Decision # 1365
Décision du Commissaire # 1365

TOPICS: B00, O00
SUJETS: B00, O00

Application No. : 2,267,070
Demande n^{o}. : 2,267,070

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 2,267,070 having been rejected under subsection 30(3) of the *Patent Rules*, has been reviewed in accordance with paragraph 30(6)(*c*) of the *Patent Rules* by the Patent Appeal Board and the Commissioner of Patents. The recommendation of the Board and the decision of the Commissioner are as follows:

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INTRODUCTION

[1] This decision deals with a review of the rejection of patent application number 2,267,070 entitled "COMPOSITIONS AND METHODS FOR IMMOBILIZING NUCLEIC ACIDS TO SOLID SUPPORTS" filed on 06 November 1997 by the Applicant Sequenom, Inc.

[2] A Summary of Reasons [SOR] was sent to the Patent Appeal Board [the Board] on 20 November 2012, which identified the following ground for rejecting this application:

X all of the claims are obvious.

[3] For the reasons that follow, we recommend that the application be refused.

BACKGROUND

[4] This application relates to compositions and methods for immobilizing nucleic acids to solid supports for use in hybridization based sequence analysis or diagnostic assays. The present description teaches array formats which feature a bead conjugated to a solid support and further conjugated to a nucleic acid. The resulting surfaces formed from the beads linked to the solid support provide an increased surface area for immobilization of nucleic acids, compared to conventional two-dimensional solid supports. An increase in the sensitivity of detection systems is achieved as the increased density of immobilized nucleic acid results in a concomitant increase in the amount of hybridizing target nucleic acid captured. This represents an improvement over conventional methods which feature the direct attachment of nucleic acids to flat solid supports.

PROSECUTION HISTORY

[5] After several Office Actions, this application was rejected in a Final Action [FA] on 28 February 2012. The application was considered defective because all of the claims were considered obvious.

[6] In response to the FA, the Applicant chose to replace the claims on file with an amended claim set containing 54 claims and continued to argue in favour of the patentability of the claims.

[7] The Examiner maintained the rejection and indicated in an SOR submitted to the Board that the Applicant had failed to overcome the obviousness defect identified in the FA.

[8] A panel of three members of the Board was established and, during the course of its review, identified certain issues that required clarification. These observations were raised with the Applicant in a letter dated 30 October 2013. In particular, the Applicant was notified of the latest practice guidelines which mandate the use of purposive construction for claim analysis. The panel also requested that the Applicant distinguish

between certain claims that appeared redundant in view of one another. Finally, the Applicant was provided a Supplemental Summary of Reasons (SSOR), prepared by the Examiner at the panel's request, to update the analysis of the obviousness defect by applying the four-step approach to assessing obviousness set out by the Supreme Court in *Apotex Inc v Sanofi-Synthelabo, Inc*, 2008 SCC 61 [*Sanofi*].

[9] The Applicant declined to provide any written submissions in response to the SOR, SSOR or the panel's letter. Instead, the Applicant chose to address the outstanding issues at an oral hearing held on 15 January 2014. In its submissions at the hearing the Applicant indicated that, in order to address the potentially redundant claims, it would be amenable to cancelling claims 40-44, 48, 52 and 53 and making claims 49-51 and 54 dependent on claim 1. The Applicant also continued to argue in favour of the patentability of the claims submitted in response to the SOR.

THE ISSUES

[10] In view of the grounds for rejection cited by the Examiner we must address the following question:

(1) Are claims 1-54 obvious?

THE CLAIMS

[11] Claims 1-54 on file contain 9 independent claims defining: compositions comprising a bead conjugated by ionic, polar or hydrophobic interaction to a solid support and further conjugated to a nucleic acid, wherein the solid support is a multiwell support comprising nanoliter wells; processes for making said compositions; kits comprising beads, insoluble supports and conjugation means for linking nucleic acids to the beads and the beads to the support by ionic, polar or hydrophobic interaction, wherein the solid support is a multiwell support comprising nanoliter wells; methods of capturing target nucleic acid using said compositions; and compositions comprising a bead bound to a solid support and further bound to a nucleic acid, wherein the solid support is a multiwell support comprising nanoliter wells. The following claims are representative of the claims under review:

1. A composition, comprising a bead conjugated by ionic, polar, or hydrophobic interaction to a solid support and further conjugated to a nucleic acid, wherein the solid support is a multiwell support comprising nanoliter wells.

8. A process of making a bead conjugated by ionic, polar, or hydrophobic interaction to a

solid support and further conjugated to a nucleic acid, comprising the steps of conjugating a bead to a nucleic acid, and conjugating a bead to a solid support, wherein the solid support is a multiwell support comprising nanoliter wells.

14. A kit, comprising:

i) beads,

ii) an insoluble support, and

iii) conjugation means for linking nucleic acids to the beads and the beads to the support by ionic, polar or hydrophobic interaction, wherein the solid support is a multiwell support comprising nanoliter wells.

16. A composition, comprising a bead conjugated to a solid support by ionic, polar, or hydrophobic interaction and further conjugated to a nucleic acid, wherein conjugation is effected with a crosslinking agent and the solid support is a multiwell support comprising nanoliter wells.

19. A composition, comprising a bead conjugated to a solid support by ionic, polar, or hydrophobic interaction and further conjugated to a nucleic acid, wherein conjugation is effected through a photocleavable linkage, and the solid support is a multiwell support comprising nanoliter wells.

30. A method of capturing target nucleic acid, comprising:

(a) contacting a target nucleic acid with beads conjugated to a solid support by ionic, polar, or hydrophobic interaction and further conjugated to a nucleic acid, wherein target nucleic acid that hybridizes to the nucleic acid conjugated to the beads is captured, and wherein the solid support is a multiwell support comprising nanoliter wells; and

(b) detecting captured target nucleic acid.

40. A method of capturing target nucleic acid, comprising:

(a) contacting a target nucleic acid with beads bound to a solid support by ionic, polar, or hydrophobic interaction and further bound to a nucleic acid, wherein target nucleic acid that hybridizes to the nucleic acid bound to the beads is captured, and wherein the solid support is a multiwell support comprising nanoliter wells; and

(b) detecting captured target nucleic acid.

45. A composition, comprising a bead bound to a solid support and further bound to a nucleic acid, wherein the solid support is a multiwell support comprising nanoliter wells.

> 48. A composition, comprising a bead conjugated to a solid support and further conjugated to a nucleic acid, wherein:
>
> the bead is conjugated to the solid support by an interaction selected from the group consisting of an ionic interaction, polar interaction and hydrophobic interaction; and
>
> the solid support is a multiwell support comprising nanoliter wells.

PURPOSIVE CONSTRUCTION

[12] Purposive construction must be done before considering the issues of validity or infringement. During purposive construction, the elements of the claimed invention are identified as either essential or non-essential: *Free World Trust v Electro Santé Inc*, 2000 SCC 66 [*Free World Trust*]. In order for an element to be considered "non-essential", "it must be shown either (i) that on a purposive construction of the words of the claim it was clearly *not* intended to be essential, or (ii) that at the date of publication of the patent, the skilled addressees would have appreciated that a particular element could be substituted without affecting the working of the invention" (*Free World Trust* at para. 55).

[13] Further, a purposive construction of the claims "requires that they be interpreted in light of the whole of the disclosure, including the specification": *Whirlpool Corp. v Camco Inc.*, 2000 SCC 67. It is also expected that one should recognize "that a patentable invention is an inventive solution to a practical problem" and "that an invention must be disclosed (and ultimately claimed) so as to provide the person skilled in the art with an operable solution": Office Patent Notice published 08 March 2013 entitled "*Practice Guidance Following the Amazon FCA Decision*" and its accompanying memo, PN 2013-02. As discussed in PN 2013-02, when determining which elements of a claim solve the identified problem it should be understood that "not every element that has a material effect on the operation of a given embodiment is necessarily essential for the operation of the invention. Some elements of a claim merely define the context or the environment of a specific working embodiment, but do not actually change the nature of the solution to the problem."

The person skilled in the art and their relevant common general knowledge

[14] In the SSOR the Examiner characterized the person of skill in the art (POSITA) as "a scientist having knowledge and skill in molecular biology and biochemistry." The SSOR also states that "[s]aid skilled person would be familiar with the common general knowledge in their field which would include compositions and methods for detecting, isolating and analyzing oligonucleotide sequences by nucleic acid hybridization."

[15] During the course of our review the panel also noted that, based on the present description the means by which a bead is conjugated to a solid support and the form of solid support would be known to the person skilled in the art as part of the common general knowledge (CGK) with regard to compositions for detecting, isolating and analyzing oligonucleotide sequences by nucleic acid hybridization. In a letter dated 30 October

2013, the panel invited the Applicant to address any of these points in writing and/or at the hearing. In its submissions at the hearing, the Applicant agreed with the Examiner's characterization of the POSITA and the CGK. Further, the Applicant acknowledged that both the means of conjugation and the forms of solid support were known. However, as shall be seen below (para. [39]), the Applicant has argued that although the individual elements in the claims were known, the inventive concept of the claims was not known.

[16] In this case, the background of the present description provides reasonable guidance as to the person(s) to whom the patent application is directed. As indicated above (para. [4]), the present application relates to compositions and methods for immobilizing nucleic acids to solid supports for use in hybridization based sequence analysis or diagnostic assays. On this basis we consider that the Examiner's characterization of the person skilled in the art as a scientist having knowledge and skill in molecular biology and biochemistry is reasonable. Further, as outlined in section 9.02.02 of the Manual *of Patent Office Practice*, the person skilled in the art is reasonably diligent in keeping up with advances in the field or fields of relevance to the invention. Therefore, the person skilled in the art to which the application is directed is to be reasonably well read as to the state of the art regarding array formats used in hybridization based sequence analysis and nucleic acid based diagnostic assays and would therefore possess the CGK acknowledged by the Applicant.

The problem and solution that the invention addresses

[17] Based on the description, the problem addressed by the claimed invention relates to improved methods of preparing solid supports containing high densities of immobilized nucleic acids for use in hybridization based sequence analysis and in diagnostic assays and provide a powerful tool for the detection, isolation and analysis of specific oligonucleotide sequences. As indicated above (para. [4]), conventional array formats feature nucleic acids linked to two-dimensional supports. The background of the description (page 3) points to several prior art references which highlight the limitations associated with these formats, namely that the density of immobilized nucleic acid is often insufficient for the ensuing analyses.

[18] Unlike conventional array formats which feature nucleic acids linked to two-dimensional supports, the solution taught by the present invention involves array formats which feature a bead conjugated to a solid support and further conjugated to a nucleic acid. Specifically, the description discloses that, by linking the nucleic acid to a bead and then linking the bead to the solid support, an increase in the density of immobilized nucleic acid is achieved by virtue of the increased surface area for binding provided by the bead.

Claim 1, purposively construed

[19] Claim 1 is directed to a composition comprising a bead conjugated to a solid support and further conjugated to a nucleic acid. In this case, the means by which the bead is conjugated to the solid support is further defined as an ionic, polar or hydrophobic interaction and the solid support is further defined as a multiwell support comprising nanoliter wells.

[20] As indicated above (para. [13]), although some elements in a claim may have a material effect on the operation of the embodiment defined by the claim, they may not have a material effect on the operation of the invention in achieving the solution to the problem, and thus may not be essential (i.e. they may be omitted or varied). With respect to claim 1 what must be considered is whether the particular means of conjugation or the type of solid support specified in the claim has any material effect on achieving the claimed solution of increasing the density of immobilized nucleic acid on a solid support by using a bead conjugated to the solid support and further conjugated to the nucleic acid.

[21] With respect to the means of conjugation, we do not consider the specific means to be an essential element. The description broadly describes that "conjugation can be through any suitable means, particularly covalent or non-covalent attachment." Further, the description does not provide any evidence that the particular conjugation means recited in the claim materially affects the operation of the claimed solution of increasing the density of immobilized nucleic acid on a solid support by using a bead conjugated to the solid support and further conjugated to the nucleic acid. Indeed, the Applicant conceded in its submissions at the hearing that, in view of claim 45 which does not identify any particular means of conjugation, the chemistry by which conjugation occurs is not essential.

[22] With respect to the type of solid support, the Applicant argued that the feature of nanoliter wells is essential. The Examiner disagreed and pointed to the description (page 4) which characterizes the solid support as being in "any desired form, including, but not limited to: a bead, capillary, plate, membrane, wafer, comb, pin, a wafer with pits, an array of pits or nanoliter wells and other geometries and forms known to those of skill in the art." On this point we agree with the Examiner: the increased density of immobilized nucleic acid is related to the increased surface area for binding provided by the bead. Further, the description does not provide any evidence that the type of solid support used is essential to achieving the solution of increasing the density of immobilized nucleic acid on a solid support by using a bead conjugated to the solid support and further conjugated to the nucleic acid.

[23] Therefore, a purposive reading of claim 1 and the specification as a whole suggests that both the means of conjugation and the type of solid support are non-essential. It follows that in the composition of claim 1, the following elements are essential to achieving the solution of increasing the density of immobilized nucleic acid on a solid support by using a bead conjugated to the solid support and further conjugated to the nucleic acid:

(i) comprising a bead

(ii) conjugated to a solid support

(iii) and further conjugated to a nucleic acid.

Other independent claims

[24] The remaining independent claims define alternative embodiments of the invention. Independent claims 8,

30 and 40 are process/method claims:

- claim 8: a process for making a bead conjugated to a solid support and further conjugated to a nucleic acid i.e., a process for making the composition defined in claim 1;
- claim 30: a method of capturing a target nucleic acid which reflects the use of the composition of claim 1, comprising contacting a target nucleic acid with beads conjugated to a solid support and further conjugated to a nucleic acid, wherein target nucleic acid that hybridizes to the nucleic acid conjugated to the beads is captured. The second step relates to detecting captured target nucleic acid; and
- claim 40: a method similar to that of claim 30, however instead of defining the beads as being "conjugated" to a solid support in claim 40 the beads are "bound" to a solid support;

whereas claims 14, 16, 19, 45 and 48 are kit and composition claims:

- claim 14: a kit comprising beads, an insoluble support and conjugation means for linking nucleic acids to the beads and the beads to the support i.e., a kit for making the composition defined in claim 1;
- claims 16 and 19: compositions similar to claim 1, except these claims place further limitations on the means of conjugation of the bead to the nucleic acid;
- claim 45: a composition similar to claim 1, however, unlike claim 1, the means by which the bead is conjugated to the solid support is not defined. The beads are also defined as being "bound" to a solid support instead of "conjugated" as defined in claim 1;
- claim 48: a composition similar to claim 1, except in claim 48 the means by which the bead is conjugated to the solid support is defined later in the claim as compared to claim 1.

[25] With respect to claims 30 and 40, which define methods of capturing a target nucleic acid, as noted above, in claim 30 the beads are "conjugated" to a solid support, as compared to claim 40 which defines the beads as being "bound" to a solid support. These are terms of the art used synonymously and interchangeably. This determination is consistent with the means defined by both of these terms. In claim 30, the beads are "conjugated" to a solid support by ionic, polar, or hydrophobic interaction. Similarly, in claim 40, the beads are "bound" to a solid support by ionic, polar, or hydrophobic interaction. The skilled person, having read the specification, would not consider that there is a material difference between "conjugated" and "bound"—they are synonyms.

Dependent claims

[26] The dependent claims add features such as characteristics of the bead, the type of nucleic acid, the order in which the bead is conjugated to the nucleic acid or solid support, the means by which the bead is conjugated to the nucleic acid, the type of detection method used. The prosecution history reveals no disagreement between the Applicant and Examiner as to the meaning or understanding of these claims.

Claim redundancy

[27] During the course of our review the panel noted that composition claims 1, 6 and 7 are directed to compositions of similar scope as those defined in claims 48, 52 and 53, respectively. For example, both claim 1 and claim 48 are directed to a composition comprising a bead conjugated to a solid support and further conjugated to a nucleic acid. Further, each of these claims defines the same means by which the bead is conjugated to the solid support and the same type of solid support. We also noted that a similar relationship appears between method claims 30, 31, 38, 35 and 36 and method claims 40, 41, 42, 43 and 44, respectively.

[28] Our letter to the Applicant requested an explanation of how the compositions of claims 1, 6 and 7 are distinct from the compositions of claims 48, 52 and 53, respectively. Similarly, the Applicant was requested to differentiate between the scope of method claims 30, 31, 38, 35 and 36 and method claims 40, 41, 42, 43 and 44, respectively. In its submissions at the hearing, the Applicant indicated that, in order to address the potentially redundant claims, it would be amenable to cancelling claims 40-44, 48, 52 and 53 and making claims 49-51 and 54 dependent on claim 1.

[29] As indicated above (para. [24]), the only difference between claim 1 and claim 48 is that the means by which the bead is conjugated to the solid support is defined earlier in claim 1 as compared to claim 48. As this is the only difference between these claims, the skilled person would see no practical distinction in their scope as each of these compositions comprises the exact same components. Therefore, claims 1 and 48 are considered to be redundant in view of one another and can be analyzed together. Similar claim groupings can be made between the following claims: claims 6 and 52; 7 and 53.

[30] A similar redundancy appears in method claims 30 and 40. With respect to these method claims, we have already identified that the only difference between claim 30 and claim 40 is that the term "conjugated" has been replaced by the synonym "bound." As this is the only difference between these claims, the skilled person would see no practical distinction in their scope as each of these method claims comprise identical steps. Therefore, claims 30 and 40 are considered to be redundant in view of one another and can be analyzed together. Similar claim groupings can be made between the following claims: claims 31 and 41; 38 and 42; 35 and 43; 36 and 44.

[31] Further, the lack of clarity in the difference in scope of the claims leads to avoidable ambiguity. It follows that the lack of clear differentiation between claims 1 and 48; 6 and 52; 7 and 53; 30 and 40; 31 and 41; 38 and 42; 35 and 43; 36 and 44, respectively, makes these claims indefinite and therefore non-compliant with subsection 27(4) of the *Patent Act*.

[32] Moreover, the multiple independent claims which have been identified as having all the same features are also considered defective for not complying with subsection 87(1) of the *Patent Rules*.

[33] Although, during its submissions at the hearing, the Applicant agreed to cancel claims 40-44, 48, 52 and 53 (and adjust dependencies accordingly), as shall be seen below, given our conclusions regarding the patentability of the claims, it is not necessary to consider a remedy for these defects.

ISSUE 1: ARE CLAIMS 1-54 OBVIOUS?

Legal Framework

[34] Section 28.3 of the *Patent Act* sets out the information that may be considered in assessing whether a claim is obvious:

> 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; and
>
> (b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.

[35] A four-step approach for assessing obviousness is set out in *Sanofi*, as follows:

(1) (a) Identify the notional "person 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 "state 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?

References Cited

[36] In the Final Action, the Examiner relied on the following references:

Publications:

Dolitzky et al., Analytical Biochemistry, 220: 257-267, 1994

O'Donnell-Maloney et al., Trends in Biotechnology, 14(10): 410-407, October 1996.

European Patent Application:

0,420,053	03 April 1991	Rudolph

Analysis under the *Sanofi* Four-Step Approach

Step 1: Identify the notional "person skilled in the art" and the common general knowledge of that person

[37] The skilled person and the common general knowledge have already been identified at paras. [14-16].

Step 2: Identify the inventive concept of the claim in question or if that cannot readily be done, construe it

[38] The SSOR states that the inventive concept of claims 1-54 is a composition comprising a bead which is used to immobilize a nucleic acid to a solid support.

[39] In its submissions at the hearing, the Applicant disputed this characterization of the inventive concept as it does not include the advantage provided by using the bead. Specifically, the use of beads to link nucleic acids to solid supports results in an increase in the density of immobilized nucleic acid on the solid support through the increased surface area for immobilization provided by the bead. The Applicant also argued that defining the solid support as a multiwell support comprising nanoliter wells was part of the inventive concept as nanoliter wells provide the benefit of being able to use small reagent volumes. On this basis, the Applicant submitted that the inventive concept of the present application "is to increase the surface area through the use of beads which are bound to the nucleic acid and also to the solid support comprising nanoliter wells." However, the Applicant also explained in its submissions following the hearing, "it is necessary to consider the entirety of the specification and claims to determine the inventive concept", citing *Sanofi*. As reasoned below, the skilled person, having read the specification, would recognize that the use of beads provides an increased surface area for immobilization of nucleic acid; however they would not consider that the feature of the solid support as a multiwell support comprising nanoliter wells forms part of the inventive concept.

[40] The present description states on page 3 that:

> "there is a need for improved methods for immobilization that provide higher densities of linked molecules for ensuing analyses. Therefore, it is an object herein to provide methods for preparing solid supports containing high densities of immobilized molecules, particularly nucleic acid molecules."

[41] The summary of the invention goes on to describe how this improvement is to be achieved:

> [c]ompositions containing at least one bead conjugated to a solid support and further conjugated to at least one molecule, particularly a nucleic acid are provided. The bead is formed from any suitable matrix material known to those of skill in the art, including those that are swellable and nonswellable. The solid support is any support known to those of skill in the art for use as a support matrix in chemical syntheses and analyses.

[42] With respect to the use of beads as compared to flat surfaces, the description indicates:

> beads linked to a solid support provide an increase surface area for immobilization of nucleic acids.

[43] Therefore, the improvement of achieving an increased density of immobilized nucleic acid is directly related to the increased surface area of the bead as compared to a two-dimensional support. This is consistent with our earlier determination that what is essential to the claimed invention of achieving an increased density of immobilized nucleic acid is the increased surface area for binding provided by the bead and not the type of solid support used (para. [22]). As indicated earlier, the form of the support was not disclosed as contributing to the solution to the problem. Further, the description is silent on the identification of a particular form of support as providing any advantage, let alone such as unexpectedly or surprisingly providing an increased surface area for binding nucleic acids. Indeed, all supports described in the present application are disclosed as being equivalent.

[44] Therefore, it is apparent from a reading of the specification as a whole that the inventive concept of the independent claims is a composition comprising a bead conjugated to a nucleic acid and further conjugated to a solid support, the bead providing an increased surface area allowing for an increased density of nucleic acid to be immobilized to the solid support. We also note that no further inventive concept(s) for the claims were identified in the SSOR, nor do any submissions from the Applicant provide an indication of any additional inventive distinguishing features in the claims. Therefore, this inventive concept applies to all of the claims.

Step 3: Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed

[45] The Examiner considered that the subject matter of claims 1-54 would have been obvious on the claim date to a person skilled in the art or science to which it pertains having regard to Dolitzky et al. or Rudolph in view of O'Donnell-Maloney et al. or common general knowledge. The Examiner cited O'Donnell-Maloney et al. as being illustrative of common general knowledge and not as forming part of the state of the art.

Dolitzky et al. and the differences therefrom

[46] In the FA, Dolitzky et al. was cited by the Examiner as disclosing:

> the synthesis of surfaces composed of polyacrolein (PA) "microspheres covalently bonded in a monolayer structure onto solid substrates such as glass, silicon crystals, and polystyrene" which remove some disadvantages associated with the use of polymeric microsphere suspensions. As suitable surfaces ELISA plates made from polystyrene are disclosed. The PA microspheres have "residual aldehyde groups ... used for covalent binding of amino ligands". Oligonucleotides are specifically disclosed as possible ligands (page 267).

[47] In response to the FA, the Applicant argued that Dolitzky et al. do not teach or suggest the multiwell supports comprising nanoliter wells as recited in the claims. Further, Dolitzky et al. do not teach or suggest conjugation of the beads to the solid support, and conjugation of the beads to nucleic acids, using ionic, polar, or hydrophobic interactions.

[48] In the SSOR the Examiner acknowledged that Dolitzky et al. do not disclose compositions comprising a bead conjugated by ionic, polar or hydrophobic interaction to a solid support, and further conjugated to a nucleic acid, wherein the solid support is a multiwell support comprising nanoliter wells. However, neither of these features forms part of the inventive concept. It has already been established that the inventive concept of the claims is a composition comprising a bead conjugated to a nucleic acid and further conjugated to a solid support, the bead providing an increased surface area allowing for an increased density of nucleic acid to be immobilized to the solid support (para. [44]). These are the features against which the state of the art needs to be assessed.

[49] As stated above, Dolitzky et al. disclose polyacrolein microspheres covalently bonded to a solid support and further covalently bonded to a ligand. Although protein ligands are exemplified, oligonucleotides are specifically disclosed as possible ligands. These novel surfaces, composed of polyacrolein nanoparticles covalently bonded in a monolayer structure onto solid substrates such as multiwell polystyrene plates, are described as significantly reducing the disadvantages of using microspheres in suspension. In particular, problems associated with microsphere suspensions include problems in separation of free ligands from ligands coupled to microspheres and instability due to agglutination (clumping together). Indeed, the Applicant argued at the hearing that although Dolitzky et al. refers to nanoparticles bound to a solid surface this was done to solve the problem of agglutination. This is true. Nevertheless, Dolitzky et al. still teach a composition comprising a polyacrolein nanoparticle conjugated to a nucleic acid and further conjugated to a

solid support.

[50] With respect to polyacrolein nanoparticles, these are considered to be a type of bead. The present description defines a bead as including "any three dimensional structure that can be conjugated to a solid support and provides an increased surface area for immobilization of biological particles and macromolecules, such as DNA and RNA." The bead is also characterized as being "made of virtually any insoluble or solid material", for example "a plastic material." Therefore, the polyacrolein nanoparticles disclosed in Dolitzky et al. are encompassed by this definition.

[51] Further, the three dimensional structure of the polyacrolein nanoparticles was recognized by Dolitzky et al. (page 257) which describes the polyacrolein nanoparticles as being spherical in nature. The polyacrolein nanoparticles are also characterized as containing a high concentration of functional groups through which ligands could be covalently coupled in a single step. Although, Dolitzky et al. do not explicitly disclose that the polyacrolein nanoparticles provide a greater surface area for binding of ligand, this property of the spherical nanoparticle is inherent in its structure. The fact that a sphere provides a greater surface area for binding ligand, as compared to a two-dimensional surface, inevitably follows from the structure of a sphere and is not a separate feature from the sphere itself.

[52] The skilled person would also consider that the increased surface area that the polyacrolein nanoparticles provide was recognized by Dolitzky et al. in view of the solution chosen to solve the problem of agglutination. Specifically, Dolitzky et al. chose to bind ligand to a surface comprising polyacrolein nanoparticles covalently bonded in a monolayer structure onto solid substrates rather than binding ligand directly to the surface of a multiwell polystyrene plate. Immobilizing the ligand directly onto a solid substrate such as a multiwell polystyrene plate would have been sufficient to prevent agglutination of ligand bound target molecules. By binding ligand to polyacrolein nanoparticles and then binding the particles to a solid substrate, not only is agglutination prevented but a high concentration of ligand can also be achieved. An increase in the amount of immobilized ligand leading to an increase in the amount of target molecule detected results in a more sensitive assay.

[53] This reasoning is consistent with the conclusions drawn by Dolitzky et al. that their studies illustrate the potential use of surfaces coated with a monolayer of functionalized nanoparticles for diagnostics and that the main advantages of these surfaces are their high binding strength, high binding stability, <u>high sensitivity</u>, <u>and ability to bind small molecules such as haptens and oligonucleotides</u>. [emphasis added]

[54] In view of the above analysis, there are no differences in the inventive concept of the claims over Dolitzky et al. Dolitzky et al. disclose polyacrolein nanoparticles conjugated to a solid support and further conjugated to a ligand, such as a nucleic acid. The polyacrolein nanoparticles, being spherical in nature, provide an increased surface area allowing for an increased density of nucleic acid to be immobilized to the solid support. Dolitzky et al. teach all of the features of the inventive concept.

Rudolph and the differences therefrom

[55] In the FA, Rudolph was cited by the Examiner as disclosing:

> solid support systems comprising support material on which particles coated with a bioaffinity agent are immobilized. Nucleic acids are mentioned as possible bioaffinity agents (page 4, lines 32-33). Covalent coupling of the coated particles to the support material is contemplated (page 4, lines 50-51). An embodiment comprising a multi-well device or microtiter plate in which dots of coated particles are placed in wells on this support material is disclosed.

[56] With respect to the coated particles being placed in wells on the support material, the Examiner interpreted this to mean that the wells actually form part of the treated support material and that the coated particles are placed in these wells forming part of the solid support.

[57] In response to the FA, the Applicant argued that Rudolph does not suggest the claimed features that the beads are conjugated to the solid support by ionic, polar or hydrophobic interaction and that the solid support is a multiwell support comprising nanoliter wells. Further the Applicant disagreed with the Examiner's interpretation that the coated particles are placed on a porous material that comprises wells. Specifically, the Applicant argued that the Examiner's interpretation that wells are formed in the support material is technically implausible. Instead, the Applicant maintained that Rudolph contemplates a support material that is flat, porous and absorbent and that multiwell plates are discussed in the context of holding the treated support material.

[58] In the SSOR the Examiner acknowledged that Rudolph does not disclose compositions comprising a bead conjugated by ionic, polar or hydrophobic interaction to a solid support, and further conjugated to a nucleic acid, wherein the solid support is a multiwell support comprising nanoliter wells. However, neither of these features forms part of the inventive concept. It has already been established that the inventive concept of the claims is a composition comprising a bead conjugated to a nucleic acid and further conjugated to a solid support, the bead providing an increased surface area allowing for an increased density of nucleic acid to be immobilized to the solid support (para. [44]). These are the features against which the state of the art needs to be assessed.

[59] Rudolph describes an improved solid support system, useful in diagnostic or other analytical assays. Unlike conventional assay formats which use a microporous matrix or a solid particle as a solid support for immobilization of a bioactive agent, as stated above, the assay support systems disclosed comprise a porous, absorbant support material on which solid particles coated with a bioaffinity agent are immobilized.

[60] Specifically, the assay support system is disclosed as being useful as a nucleic acid probe, with the appropriate ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) as the bioaffinity agent. With respect to suitable particulate materials for binding of bioaffinity agents, Rudolph discloses that microspheres or beads are preferred, with polystyrene latex beads being exemplified.

[61] At the hearing the Applicant argued that, although Rudolph discloses particles coated with a bioaffinity agent, the inventive concept of using a bead to increase surface area was not disclosed or suggested. A review of Rudolph reveals that there is no explicit teaching or disclosure that the solid particles provide a greater surface area for binding of bioaffinity agent.

[62] However, as indicated above (para. [50]), the present description defines a bead as including "any three dimensional structure that can be conjugated to a solid support and provides an increased surface area for immobilization of biological particles and macromolecules, such as DNA and RNA." Further, the bead "can be made of virtually any insoluble or solid material", for example "a plastic material." Notably, the polystyrene latex beads disclosed in Rudolph are encompassed by this definition.

[63] Although Rudolph does not explicitly disclose that the polystyrene latex beads provide a greater surface area for binding of ligand, this property of the bead is inherent in its structure. The fact that the bead provides a greater surface area for binding ligand, as compared to a two-dimensional surface, inevitably follows from the structure of the bead and is not a separate feature from the bead itself.

[64] The skilled person would also consider that the increased surface area that the polystyrene latex beads provide was recognized by Rudolph as one of the objects of their invention was to provide a highly sensitive assay which can detect low levels of target molecule. Indeed, an increase in assay sensitivity was demonstrated through a direct comparison between this improved assay format and a standard microtiter plate coated with antibody. Significantly, the detection limit achieved using a porous, absorbant support material on which polystyrene latex beads coated with antibody were immobilized was up to 10 times more sensitive than using antibody coated microtiter plate technology. As the method of detection did not change, the increased sensitivity can be directly attributed to a higher density of immobilized probe. An increase in the amount of immobilized probe would be expected to lead to an increase in the amount of target molecule detected resulting in a more sensitive assay. In turn, the higher density of immobilized probe can be directly attributed to the increased surface area for binding provided by the spherical nature of the polystyrene latex beads.

[65] In view of the above analysis, there are no differences in the inventive concept of the claims over Rudolph. Rudolph discloses polystyrene latex beads conjugated to a solid support and further conjugated to a ligand, such as a nucleic acid. The polystyrene latex beads, being spherical in nature, provide an increased surface area allowing for an increased density of nucleic acid to be immobilized to the solid support. Rudolph teaches all of the features of the inventive concept.

Summary of differences

[66] We find that the Dolitzky et al. or Rudolph, each taken independently disclose all of the features of the inventive concept of the claims.

Step 4: 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?

[67] There are no differences between the "state of the art" and the inventive concept of the claims. Therefore, the skilled person based on the teachings of either Dolitzky et al. or Rudolph would see no inventive step in preparing a composition comprising a bead conjugated to a nucleic acid and further conjugated to a solid support, the bead providing an increased surface area allowing for an increased density of nucleic acid to be immobilized to the solid support. It follows that the independent claims are obvious.

[68] As indicated above (para. [44]), no further inventive concept(s) for the claims were identified by the Examiner or the Applicant. However, for the sake of completeness, we will address whether any additional features in the dependent claims are inventive.

Dependent claims

[69] The additional features in the dependent claims would be within the common general knowledge of the person skilled in the art, namely: characteristics of the bead, the type of nucleic acid, the order in which the bead is conjugated to the nucleic acid or solid support, the means by which the bead is conjugated to the nucleic acid, the type of detection method used. This determination is consistent with the Applicant's acknowledgement (para. [15]) that the individual elements in the claims are part of the common general knowledge of the person skilled in the art. Further, as indicated above (para. [44]), the Applicant did not argue any particular inventive aspects of these claims.

[70] The skilled person based on their common general knowledge would see no inventive step in further characterizing the bead, defining the order in which the bead is conjugated to the nucleic acid or solid support or placing limitations on the type of nucleic acid, the means by which the bead is conjugated to the nucleic acid or the type of detection method used. Given that the skilled person would understand these features to be lacking any degree of invention, it follows that the dependent claims are obvious having regard to either Dolitzky et al. or Rudolph in view of common general knowledge.

Conclusions

[71] Claims 1-54 are obvious having regard to either Dolitzky et al. or Rudolph in view of common general knowledge.

Non-essential features argued by the Applicant

[72] Although we have concluded that there are no differences between the inventive concept of the claims and the state of the art, the Applicant argued that neither Dolitzky et al. or Rudolph disclosed the features that the

bead is conjugated by ionic, polar or hydrophobic interaction to a solid support, or a solid support that is a multiwell support comprising nanoliter wells. Although the Examiner acknowledged these features were not taught by either of the cited references, the Examiner argued that these differences would have been obvious in view of O'Donnell-Maloney et al. or common general knowledge. Even though it is not strictly necessary to do so, we will now address whether these features are inventive.

Means of conjugation and type of solid support

[73] We have already established that the common general knowledge of the skilled person includes knowledge of the means by which a bead is conjugated to a solid support and the various forms of solid support with regard to compositions for detecting, isolating and analyzing oligonucleotide sequences by nucleic acid hybridization.

[74] With respect to the means of conjugation, we note that both Dolitzky et al. and Rudolph disclose covalent attachment of a bead to a solid support. Notably, the present description discloses covalent attachment as a preferred embodiment and lists the formation of a covalent bond as being among the preferred means of conjugation which also include: streptavidin or avidin to biotin interaction; hydrophobic interaction; magnetic interaction; and, polar interaction. Given that the POSITA is aware of these various means of conjugation and the fact that the present description does not demonstrate any surprising advantage to limiting the type of conjugation to ionic, polar or hydrophobic, choosing a particular means of conjugation lacks an inventive step. Indeed, this is consistent with the Applicant's own acknowledgement that, in view of claim 45 which does not specify any specific means of conjugation, the chemistry by which conjugation occurs is not essential to the invention (para. [21]).

[75] With respect to the type of solid support, the review article by O'Donnell-Maloney et al. discusses the development of densely packed array formats for DNA sequence and analysis. Specifically, O'Donnell-Maloney et al. recognize that it is desirable to increase the sensitivity of the detection systems and that this can be achieved by increasing the amount of immobilized probe on the array. Also, if the sensitivity of the detection system can be improved, more data can be obtained from each experiment because a higher density of smaller sample spots can be used. Microtiter plates are specifically disclosed as an array format which allows for high throughput hybridization detection. It would have been *prima facie* obvious to the POSITA that immobilizing a probe in a smaller sample spot, such as a nanoliter well, would not only allow for the detection of smaller amounts of target molecule but also allow for the use of smaller reagent volumes. This assay format would be particularly useful for high throughput assays where the amount of target molecule to be detected is limiting or reagent costs are high. In the absence of any comparative data demonstrating a surprising advantage to limiting the type of solid support to a multiwell support comprising nanoliter wells, this particular assay format is also considered non-inventive.

Conclusion

[76] In view of the above, the skilled person based on their common general knowledge would see no inventive step in limiting the particular means by which the bead is conjugated to a solid support to ionic, polar or hydrophobic interaction, or in limiting the type of solid support to a multiwell support comprising nanoliter wells. Given that the skilled person would understand these limitations to be lacking any degree of invention, it follows that even if they were essential, they would not overcome the conclusion that the claims are obvious.

RECOMMENDATION OF THE BOARD

[77] We recommend that the application be refused for lack of compliance with section 28.3 of the *Patent Act*, since the claims are obvious.

Christine Teixeira	Paul Sabharwal	Andrew Strong
Member	Member	Member

DECISION OF THE COMMISSIONER

[78] I concur with the findings and the recommendation of the Board. I hereby refuse the application.

[79] Under section 41 of the *Patent Act*, the Applicant has six months within which to appeal my decision to the Federal Court of Canada.

Sylvain Laporte

Commissioner of Patents

Dated at Gatineau, Quebec,

this 28th day of April, 2014