

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 28

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte THOMAS J. MERCOLINO and VIRENDRA O. SHAH

Appeal No. 1997-2513
Application No. 08/206,917

ON BRIEF

Before ROBINSON, SPIEGEL, and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-6 and 8-12, which are all the claims pending in the application.

Claims¹ 1 and 5 are illustrative of the subject matter on appeal and are reproduced below:

1. A method for determining instrument event-counting linearity of a flow cytometer comprising the steps of:
 - (a) separating a sample of cells into at least two aliquots;
 - (b) adding equal volumes of mixtures containing known concentrations of fluorescent microparticles in a diluent to each aliquot, wherein the concentration of microparticles added to each aliquot differs;
 - (c) counting the number of microparticles added to each aliquot by means of flow cytometry; and
 - (d) performing statistical analysis on the number of microparticles counted from all aliquots to determine linearity.

5. In a method for absolute counting of cells in a sample wherein the sample comprises cells mixed with one or more cell markers having an emission spectra and a known number of a first fluorescent microparticle having an emission spectra, wherein the emission spectra of the cell markers and the first microparticle are distinguishable, a method comprising the steps of:
 - (a) separating the sample into at least two aliquots;
 - (b) adding equal volumes of mixtures containing known concentrations of a second fluorescent microparticle in a diluent to each of the aliquots, wherein the concentration of second fluorescent microparticles added to each aliquot differs and wherein the second microparticle has an emission spectra which is distinguishable from the emission spectra of the first microparticle and cell markers;
 - (c) counting the number of fluorescent cells, the number of first microparticles and the number of second microparticles in each aliquot by means of flow cytometry; and
 - (d) performing statistical analysis on the number of cells counted, the number of first microparticles counted and the number of second microparticles counted in all aliquots to determine linearity.

Claim 12 is drawn to the method of claim 5, wherein the cell markers comprise monoclonal antibodies labeled with carbocyanine, a fluorescent dye.

¹ We note that the numbering of claims 7-11 as listed in the Appendix of appellants' Brief is incorrect. Claim 7 has been canceled. Therefore, claims 7-11 should be numbered 8-12, respectively.

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The references relied upon by the examiner are:

| | | |
|--------------------------|-----------|---------------|
| Valet | 4,751,188 | Jun. 14, 1988 |
| Brosnan et al. (Brosnan) | 4,987,086 | Jan. 22, 1991 |
| Schwartz | 5,093,234 | Mar. 3, 1992 |

Stewart et al. (Stewart), "Quantitation of Cell Concentration Using the Flow Cytometer," Cytometry, Vol. 2, No. 4, pp. 238-43 (1982)

GROUNDINGS OF REJECTION²

Claims 1-4 stand rejected under 35 U.S.C. § 103 as being unpatentable over Stewart.

Claims 5, 6 and 8-11 stand rejected under 35 U.S.C. § 103 as being unpatentable over Stewart in view of Schwartz and Brosnan.

Claim 12 stands rejected under 35 U.S.C. § 103 as being unpatentable over Stewart in view of Schwartz, Brosnan and Valet.

Claims 1-6 and 8-12 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 48 of co-pending Application No. 08/046,343.³

² We note the examiner withdrew her final rejections under 35 U.S.C. § 112, first, second and fourth paragraphs in the Advisory Action, mailed January 27, 1995 (Paper No. 16).

³ We note that Application No. 08/287,759 ('759) is a file wrapper continuation of 08/046,343, which is a file wrapper continuation of 07/570,569. The '759 application issued as United States Patent No. 5,627,037 on May 6, 1997. Therefore, this obviousness-type double patenting rejection is no longer provisional.

We reverse the rejection of claims 5, 6 and 8-11, and the rejection of claim 12 under 35 U.S.C. § 103. We affirm the rejection of claims 1-4 under 35 U.S.C. §103 and the obviousness-type double patenting rejection.

DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, and to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer⁴ for the examiner's reasoning in support of the rejections. We further reference appellants' Brief⁵, and appellants' Reply Brief⁶ for the appellants' arguments in favor of patentability.

CLAIM GROUPING:

Appellants argue (Brief, page 3) that “[c]laims 1-4 are directed to a method for determining event-counting linearity of a flow cytometer. Claims 5-6 and 8-12 are directed to a method for absolute counting of cells by flow cytometry.” In addition, claims 5, 6 and 8-11 stand rejected on a different ground than claim 12. Therefore, we interpret these statements as setting forth three groups (1) claims 1-4, (2) claims 5-6 and 8-11 and (2) claim 12. Accordingly, we limit our discussion to claims 1, 5 and 12. Furthermore, claims 2-4 stand or fall

⁴ Paper No. 22, mailed February 7, 1996.

⁵ Paper No. 21, received October 5, 1995.

⁶ Paper No. 24, received March 4, 1996.

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together with claim 1 and claims 6 and 8-11 stand or fall together with claim 5. 37
CFR §1.192(c)(7)(1995).

THE REJECTIONS UNDER 35 U.S.C. § 103:

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

Claims 1-4:

The examiner argues (Answer, page 4) that Stewart teaches “a method for quantitating cell concentration using a flow cytometer wherein the method comprises adding to several aliquots of fluorescently stained cell samples either red fluorescent microspheres or green fluorescent microspheres of known concentration and whose emission spectra are differentiable from each other and the sample.” According to Stewart (Abstract), “[s]ince the [fluorescent micro] particle concentration is known, the number of [fluorescent micro] particles that have accumulated gives the exact volume of the sample analyzed.” The examiner argues (Answer, page 4) that while Stewart “does not teach adding equal volumes of known concentration to each of the samples wherein the concentration of microparticles added to each sample is different,” Stewart teaches “on page 240 that statistical analyses was performed on the results from all aliquots to determine linearity.”

The examiner concludes (Answer, page 5) that “[i]t would have been obvious to the ordinarily skilled artisan at the time the invention was made to have added equal volumes of known concentration to each of the samples wherein the

concentration of microparticles added to each sample is different.” The examiner takes (Answer, page 5):

Official Notice of the equivalent function of a method which comprises adding different volumes of particles of the same concentration to obtain a different particle count and adding the same volume of material having different concentrations to obtain a different particle count and the use of either method to obtain a different particle count would have been within the level of ordinary skill in the art absent a showing of unexpected results.

In response appellants argue (Brief, page 7) “the rejection should be overturned in view of ... MPEP 706.02(a) ... ‘if the [a]ppellant traverses such an assertion, the [e]xaminer should cite a reference in support of his or her position.’” Appellants assert (Brief, bridging sentence, pages 7-8) that no reference was provided in response to their previous traversal of this rejection. However, the examiner argues (Answer, page 10) with reference to Stewart that:

total particle count is equal to the concentration of the particles times the volume of particles ... $T_p = C_p V_p$. Therefore, equating T_{p1} to T_{p2} ... if one varies C_{p1} and maintains V_{p1} constant, one can vary V_{p2} and maintain C_{p2} constant to obtain $T_{p1} = T_{p2}$. [Footnote omitted].

Appellants agree (Reply Brief, bridging paragraph, pages 2-3) with the examiner that “total particle count can be varied by maintaining a constant concentration and varying the volume of the particles or alternatively, by maintaining a constant volume and varying the concentration.” However, appellants dispute (Reply Brief, page 3) “that the methods are ‘equivalent’ with respect to the instant invention.” Appellants argue (Reply Brief, page 3) that “the method of Stewart et al, while clearly being able to produce varying concentrations of particles by varying the volumes, is nowhere near as useful” as the claimed invention. Appellants reason (Reply Brief,

page 3) that since flow cytometry utilizes constant volumes of materials, the Stewart method would require “large volumes” or “enormously large quantities of dilutant” to obtain low concentrations of particles, particularly at or near zero. The examiner argues (Answer, page 11) that “the mere allegations by appellant [sic] that achieving a claimed element by a known method would be ‘difficult’ is not sufficient evidence that such a limitation could not be achieved,... [Furthermore] end point calibrations are extremely well known in the art in order to prove the soundness of any instrument to be used in experimentation.” We agree with the examiner. We also note the following disclosures in Stewart (page 242) “[t]he number of microspheres should be kept to a small proportion of the total events analyzed” and:

To determine that the counting methodology was linear over a wide range of microsphere concentrations, stained CHO cells ... were adjusted to 7.5×10^5 ($\pm 10\%$) cells/ml. Varying amounts (μl) of green or red fluorescent spheres from stock solutions were added to the cell samples. Since the CHO cell concentration was known, CHO cells were used to determine the concentration of microspheres in the cell samples using the flow cytometer. The results in Figure 1 show that for every combination tested a linear relationship exists between the volume (μl) of spheres added and the concentration of spheres measured in the cell samples [Stewart, page 240].

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). The examiner has demonstrated, and appellants agree, that it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was

made that total particle count can be varied by maintaining a constant concentration and varying the volume of the particles, or alternatively, by maintaining a constant volume and varying the concentration. While appellants argue that the claimed method is not equivalent to that of Stewart, appellants failed to establish why it would not have been prima facie obvious to modify the teachings of Stewart in the manner urged by the examiner. Therefore, we find no error in the examiner's rejection. Accordingly, we affirm the examiner's rejection of claim 1 under 35 U.S.C. § 103 over Stewart. As discussed supra, claims 2-4 fall together with claim 1.

Claims 5, 6 and 8-11:

The examiner argues (Answer, page 6) that:

Stewart et al. does not teach the addition of more than one set of microbeads to the sample, nor the use of fluorescently labelled monoclonal antibodies as cell markers.

Schwartz teaches a flow cytometer calibration sample containing more than one type of microparticles, i.e. microparticles dyed with different fluorescent dyes and/or that are dyed with multiple fluorescent dyes. The differently dyed microparticles are distinguishable from each other.

The examiner concludes (Answer, page 6) that “[i]t would have been obvious ... to have added more than one set of microbeads to each aliquot of the sample of Stewart et al. as taught by Schwartz in order to simultaneously calibrate two or more fluorescence intensities of a flow cytometer having more than one fluorescence channel.” Appellants argue (Brief, page 10) that “Schwartz ... specifically provides that the fluorescent dyes attached ‘will have excitation and emission spectra that match the spectra of the specific fluorescent dyes used to label the sample to be

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measured on the flow cytometer'" Appellants contrast Schwartz (Brief, page 10) from the instant invention which requires that "the emission spectra of the cell markers and fluorescent microparticle are distinguishable (i.e., not matched)...."

The examiner does not find appellants' argument persuasive. The examiner argues (Answer, page 12) that "Stewart ... teaches that the fluorescent particles have different emission spectra from each other and the sample." We are not persuaded by the examiner's position.

As set forth in Ecolchem Inc. v. Southern California Edison, 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075 (Fed. Cir. 2000) the:

"suggestion to combine may be found in explicit or implicit teachings within the references themselves, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved." ... However, there still must be evidence that "a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." ... "[A] rejection cannot be predicated on the mere identification ... of individual components of claimed limitations. Rather particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.".... [Citations omitted].

On this record, Schwartz discloses (claim 1) a method of aligning, compensating and/or calibrating a flow cytometer. Schwartz discloses (column 8, line 48 to column 9, line 16) that it is important to use beads having the same emission spectra as the sample in order to "perform accurate compensation adjustments." In contrast, Stewart teaches (abstract) "[a] simple procedure ... to simultaneously measure cell concentration and analyze marker positive cell populations...."

While the examiner suggests (Answer, page 12) that Stewart teaches particles having different emission spectra, the examiner does not explain why one of ordinary skill in the art would select the necessary elements from Schwartz for combination with Stewart in the manner claimed by appellants. We remind the examiner that “a rejection cannot be predicated on the mere identification ... of individual components of claimed limitations. Rather particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.” See Ecolochem 227 F.3d at 1375, 56 USPQ2d at 1075.

Bronsan, relied on by the examiner (Answer, page 7) “for the fact that it is known to detect T-cells that bear CD3 antigens using flow cytometry analysis techniques,” fails to make up for the deficiencies in the combination of Stewart in view of Schwartz.

Therefore, in our opinion, the examiner failed to meet her burden of establishing a prima facie case of obviousness. Accordingly, we reverse the examiner’s rejection of claims 5, 6 and 8-11 under 35 U.S.C. § 103 over Stewart in view of Schwartz and Bronsan.

Claim 12:

According to the examiner (Answer, page 7) “Valet teaches a method for the simultaneous quantitative determination of cells using a flow cytometer. Valet further teaches that carbocyanines are well known fluorescent dyes used in flow cytometry analysis techniques.” The examiner therefore combines Valet with the teachings of Stewart, Schwartz and Bronsan finding (Answer, page 8) that “[i]t would

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have been obvious ... to have used a carbocyanine dye in the method of Stewart et al. as modified by Schwartz and Brosnan et al.”

Appellants argue (Brief, page 11) that Valet does not remedy the deficiency of the combination of Stewart, Schwartz and Brosnan, see supra. We agree. Accordingly, we reverse the examiner’s rejection of claim 12 under 35 U.S.C. § 103 over the combination of Stewart, Schwartz, Brosnan and Valet.

Obviousness-type Double Patenting:

Appellants do not argue the merits of this rejection. Instead, appellants expressly state (Brief, page 6) that “[a]ppellants stand ready to terminally disclaim the instant [a]pplication upon issuance of the co-pending [a]pplication as a patent.”

Since no terminal disclaimer has been submitted to overcome this rejection, we affirm the examiner’s rejection of claims 1-6 and 8-12 under the judicially created doctrine of obviousness-type double patenting.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

DOUGLAS W. ROBINSON)
Administrative Patent Judge)
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)
) BOARD OF PATENT
CAROL A. SPIEGEL)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES

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