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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte EDUARDO MARBAN and KE CHENG

Appeal 2019-004542
Application 14/437,812
Technology Center 1600

Before RICHARD M. LEBOVITZ, ULRIKE W. JENKS, and JAMIE T. WISZ, *Administrative Patent Judges*.

WISZ, *Administrative Patent Judge*.

DECISION ON APPEAL

STATEMENT OF THE CASE

Pursuant to 35 U.S.C. § 134(a), Appellant[1] seeks review of claims 19, 51, 52, 54, 59, 60, and 67–71. We have jurisdiction under 35 U.S.C. § 6(b).

For the reasons set forth below, we AFFIRM.

CLAIMED SUBJECT MATTER

The Specification describes therapeutic cell populations, comprising cardiosphere-derived cells (CDCs) that are substantially depleted of CD90. Spec. ¶¶ 2, 9. These CDCs may be used for cardiac tissue repair or regeneration. *Id.* ¶ 60.

Claims 19 and 70 are independent claims. Claim 19 is illustrative and is set forth below:

> 19. A composition of therapeutic cells comprising cardiosphere-derived cells (CDCs) substantially depleted of cells expressing the CD90 cell marker, wherein said CDCs are a mixed population of cells obtained by culturing cardiospheres (CSps) as an adherent monolayer culture on a solid surface of a culture vessel.

Appeal Br. 27 (Claims Appendix).

REJECTIONS

The Examiner rejected claims 19, 51, 52, 54, 59, 60, and 67–71 under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real parties in interest as Cedars-Sinai Medical Center and Capricor Therapeutics, Inc. Appeal Br. 3.

The Examiner rejected claims 68 and 69 as indefinite under 35 U.S.C. § 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph.

The Examiner rejected claims 19, 51, 54, 59, 67, 70, and 71 under 35 U.S.C. § 102(b) as anticipated by Haag.[2]

The Examiner rejected claims 19, 51, 52, 54, 67, 70, and 71 under 35 U.S.C. § 102(b) as anticipated by Smith.[3]

The Examiner rejected claims 52 and 60 under 35 U.S.C. § 103(a) as obvious over Haag.

The Examiner rejected claims 19, 51, 52, 54, 59, 60, 67, 70, and 71 under 35 U.S.C. § 103(a) as obvious over Marban[4] in view of Haag and Kisselbach.[5]

ISSUES AND ANALYSIS

Claim Construction of "Cardiosphere-Derived Cells"

The Examiner construes the claim term "cardiosphere" as meaning "an aggregate of cardiac-derived cells" and the claim term "cardiosphere-derived cells" ("CDC") as meaning "any cell that has a cardiosphere as its origin and thus includes any cell that a cardiosphere can be differentiated

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[2] Haag et al., US 2010/0040587 A1, published Feb. 18, 2010 ("Haag").
[3] Smith et al., Unique Phenotype of Cardiospheres Derived from Human Endomyocardial Biopsies, Circulation, Vol. 112, No. 17, Suppl. S., (2005) ("Smith").
[4] Marban et al., US 2008/0267921 A1, published Oct. 30, 2008 ("Marban").
[5] Kisselbach et al., CD90 Expression on human primary cells and elimination of contaminating fibroblasts from cell cultures, Cytotechnology, 59:31–44 (2009) ("Kisselbach").

into including cardiac progenitor cells and mature cardiac cells." Final Act. 4.

Appellant asserts that the meaning of CDCs, as used in the claims, "is consistent with how the term is generally understood in the art – *i.e.*, a population of cells not found in nature and produced via particular *in vitro* process steps which are also recited in the claims." Appeal Br. 5. According to Appellant, the Specification "teaches that both cardiospheres and CDCs are a number of steps removed from naturally occurring cell populations as found in, for example, a tissue biopsy." *Id.* at 9 (citing Spec. ¶¶ 66, 67, 70, 71, 73, 74). In support of this claim construction, Appellant cites to the Declaration of Rachel Smith, Ph.D., dated November 9, 2017 ("the Smith Declaration"), which states that:

> from the application as filed and the state of the art, one of ordinary skill in the art understood that CDCs were comprised [of] a mixed population of cells having various collective properties of a particular cell population as a whole [that can be objectively compared against other cell populations].

Id. at 9–10 (alterations in original) (citing Smith Declaration ¶ 3[6]).

We are not persuaded by Appellant's arguments. "[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000). We agree with the Examiner that, under the broadest reasonable interpretation, the claim term "cardiospheres" should be

[6] Although Appellant cites to paragraph 3 of the Smith Declaration, the quoted language appears in paragraph 8.

construed as "an aggregate of cardiac-derived cells" and "cardiosphere-derived cells" can be any cells that have cardiospheres as their origin. Cardiosphere-derived cells (CDCs) are not explicitly defined in the Specification and the Examiner's claim interpretation is not inconsistent with how the term is used in the Specification.

Appellant appears to argue that CDCs, as recited in the claims, should be interpreted more narrowly to include only those cells that are produced by specific process steps described in the Specification at paragraphs 66, 67, 70, 71, 73, and 74. Appeal Br. 8–9. First, we find that CDCs are not so narrowly defined in the Specification, which only describes the disclosed process steps as "embodiments." *See* Spec. ¶¶ 66, 67, 70, 73, 74. Second, it is not appropriate to import limitations from the Specification into the claims. "Limitations in the specification not included in the claim[s] may not be relied upon to impart patentability to an otherwise unpatentable claim." *In re Lundberg*, 244 F.2d 543, 548 (CCPA 1957); *Silicon Graphics, Inc. v. ATI Techs., Inc.,* 607 F.3d 784, 792 (Fed. Cir. 2010) ("A construing court's reliance on the specification must not go so far as to import limitations into claims from examples or embodiments appearing only in a patent's written description unless the specification makes clear that the patentee intends for the claims and the embodiments in the specification to be strictly coextensive." (internal quotation marks omitted)).

Third, Appellant acknowledges that including the experimental conditions from the Specification in the claims, "would exclude CDCs that were made using slightly different conditions from the scope of the claims."

Reply Br. 4. We agree with Appellant that the term CDCs should not be so narrowly defined.

Appellant also argues that CDCs are a population of cells and the Examiner is inappropriately interpreting the phrase "cardiosphere-derived cells" as ***any single cell*** that has a cardiosphere as its origin at some point in time and thus includes any single cell that a cardiosphere can be differentiated into. Appeal Br. 6. We are not persuaded by this argument because the claim construction applied by the Examiner does include a mixed population of cardiac cells and, therefore, is not inconsistent with Appellant's assertion that the claims encompass such a mixed composition. We are similarly not persuaded by the Smith Declaration because it merely states that CDCs are "comprised [of] a mixed population of cells having various collective properties of a particular cell population as a whole," which are encompassed by the adopted claim construction. Smith Declaration ¶ 8.

Rejection of claims 19, 51, 52, 54, 59, 60, and 67–71 under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter.

The Examiner finds that claims 19, 51, 52, 54, 59, 60, and 67–71 are directed to a judicial exception without significantly more. Final Act. 3. Specifically, the Examiner finds that the claims "recite a judicial exception because CD90 negative cells derived from a cardiosphere from cardiac tissue are not found to be markedly different from naturally occurring cells present in cardiac tissue, i.e., cells are a natural phenomenon." *Id.* at 5. The Examiner further finds that "[t]here is no evidence on the record that distinguishes the claimed CDCs that are negative for CD90 from those

CD90 negative cells naturally present in cardiac tissue." *Id.* In support of this position, the Examiner cites to Haag. The Examiner finds that Haag teaches therapeutic cardiac cells, which are isolated from a primary culture, and are CD90 negative. *Id.* (citing Haag ¶¶ 10, 25, 30). According to the Examiner, cells in primary cell cultures, such as those disclosed in Haag, "are well known to closely represent the in vivo state and generate more relevant data representing living systems and therefore the CD90 negative . . . cardiac cells of Haag that appear to be indistinguishable from Applicant's claimed cells are also representative of cardiac cells found in vivo." *Id.*

Lastly, the Examiner finds that "[t]he claims do not include additional elements that are sufficient to amount to significantly more than the judicial exception because there is no apparent difference between applicant's claimed isolated solution and the naturally occurring components." *Id.*

Appellant asserts that the cell population disclosed in Haag and in nature are distinguishable from the claimed CDCs depleted of CD90 positive cells. Appeal Br. 11–17. According to Appellant, there are certain differences in how the Haag cell population is obtained vis-à-vis the process limitations of the claims and there are structural differences between CDCs and the Haag cell population. *Id.* at 13. Specifically, while Appellant acknowledges that steps a) through c) of Haag are the same as the process steps described in the Specification at paragraphs 66–68 and 70, Appellant asserts that Haag "lacks any description of the ***subsequent*** *in vitro* manipulation of cardiosphere-forming cells to derive (e.g., produce) cardiospheres, or the subsequent *in vitro* manipulation of cardiospheres to derive CDCs." *Id.* at 14 (citing Haag ¶¶ 13–14; Spec. ¶¶ 71, 73, 74).

Appellant further contends that "[a]ssuming *arguendo* that the Haag cell population is a suitable substitute for the cell population naturally present in the human heart . . . there is extensive experimental data in [Kreke][7] showing certain structural differences between CDCs vis-à-vis the Haag cell population." *Id.* at 15. According to Appellant, Table 12 of Kreke demonstrates that the Haag cell population (equivalent to the Explant-Derived Cells, or EDCs, of Kreke), "are clearly a different cell population than ***CDCs*** having various average marker expression levels that can be directly compared under the same experimental conditions." *Id.* at 15–16. Appellant concludes:

> Kreke's experimental data shows certain structural differences between EDCs and CDCs, *i.e.*, between the Haag cell population and CDCs. Based on this difference, a person of ordinary skill in the art would reasonably conclude that there would be corresponding structural differences between the Haag cell population and CDCs substantially depleted of CD90 positive cells according to Claims 19 and 70, because the makeup of CDCs would remain the same except for the removal of CD90 positive cells.

Id. at 16.

Appellant further contends that the Specification "demonstrates that the population of CDCs substantially depleted of CD90 positive cell subpopulation has improved potency in repair of damaged heart tissue." *Id.* (citing Spec. Figs. 14, 17, 20–28). According to Appellant, based on these improved results, "the recited population of '[CDCs] substantially depleted

[7] Kreke et al., WO 2013/184527 A1, published Dec. 12, 2013 ("Kreke").

of cells expressing the CD90 cell marker' are significantly more and should be subject matter eligible." *Id.* at 16–17.

In performing an analysis of patentability under Section 101, we follow the framework set forth by the Supreme Court in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012). We are also mindful of, and guided by, the United States Patent and Trademark Office's 2019 Revised Patent Subject Matter Eligibility Guidance, 84 Fed. Reg. 50 (January 7, 2019) (the "Guidance").

Following the first step of the *Mayo* framework, we find that claim 19 recites a composition of matter and therefore falls into one of the broad statutory categories of patent-eligible subject matter under 35 U.S.C. § 101.

In the next step of the *Mayo* analysis, we determine whether the claim at issue recites a nonstatutory, patent-ineligible concept, i.e., a law of nature, a phenomenon of nature, or an abstract idea. *Mayo*, 566 U.S. at 70–71; Guidance 54 (step 2A, Prong 1). If we determine that the claim recites a judicial exception, we then determine whether the limitations of the claim reciting the judicial exception are integrated into a practical application. *Id.* (Step 2A, Prong 2). Finally, if we determine that the claim is directed to a judicially-created exception to Section 101, we evaluate the claims under the next step of the *Mayo* analysis, considering the elements of each claim both individually and "as an ordered combination" to determine whether additional elements "transform the nature of the claim" into a patent-eligible application. *Mayo*, 566 U.S. at 78–79; Guidance at 56 (Step 2B).

A. Guidance Step 2A, Prong 1

Claim 19 recites, in relevant part: "A composition of therapeutic cells comprising cardiosphere-derived cells (CDCs) substantially depleted of cells expressing the CD90 marker . . . ." Haag discloses CD90 negative cardiac cells obtained from heart muscle biopsies, establishing that such cells exist in natural heart muscle. Haag, code (57), ¶ 11. Appellant asserts that the CDCs of the invention are "a number of steps removed from naturally occurring cell populations as found in, for example, a tissue biopsy." Appeal Br. 9. As discussed above, "cardiosphere-derived cells" can be any cells that have cardiospheres (i.e., cardiac-derived cells) as their origin. By definition, cardiospheres are comprised of cells found in natural heart tissue. Smith, Abstract. The only further limitation in the claim is that the CDCs are "substantially depleted of cells expressing the CD90 marker." As shown by Haag, cardiac cells lacking CD90 can be obtained from heart muscle biopsies. Haag, code (57). The claim also recites that "said CDCs are a mixed population of cells obtained by culturing cardiospheres (CSps) as an adherent monolayer culture on a solid surface of a culture vessel." However, since claim 19 is a product-by-process claim, the claim is not limited to cells obtained by the recited manipulative steps, but only to the structure of the cell obtained by the steps. *See* MPEP § 2113. As discussed below, Appellant has not persuasively shown that the claimed CDCs obtained by culturing cardiospheres as an adherent monolayer culture on a solid surface of a culture vessel are structurally different from native cardiac-derived cells.

Isolating a natural product and thereby creating a non-naturally occurring material does not necessarily result in patent-eligible subject matter. *See Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 593 (2013). In *Myriad*, the Supreme Court held claims directed to isolated DNA were not "saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule." 569 U.S. at 593. Rather, to be patent eligible, a "nonnaturally occurring manufacture or composition of matter" must possess "markedly different characteristics from any found in nature." *Id.* at 590–91 (citing *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)).

As discussed above, Appellant argues that the cell population of the claimed invention is structurally different than the cells disclosed in Haag as evidenced by Kreke. However, we agree with the Examiner that the evidence cited by Appellant is not commensurate in scope with the claims. The cell population disclosed in Kreke undergoes many process steps with specific culture methods and specific culture times that are not recited in the claims. The only step required by claim 19 is that the population of cells is obtained by culturing cardiospheres as an adherent monolayer culture on a solid surface of a culture vessel. Appellant also has not persuasively shown that the claimed CDCs, which are obtained using this process step, are a transformation of the natural product, or that they have properties not possessed by naturally-occurring cardiac or cardiosphere cells. Consequently, we are not persuaded that the claimed CDCs are markedly different from the natural product and we find that the claims recite a judicial exception, i.e., a product of nature.

B. Guidance Step 2A, Prong 2

Having determined that the claims recite a judicial exception, we next consider whether the claims integrate the judicial exception into a practical application. "[I]ntegration into a practical application" requires that the claim recite an additional element or a combination of elements, that when considered individually or in combination, "apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial exception." Guidance at 54.

Here, there is no practical integration of the natural product. Claim 19 recites a composition of cells, which have the natural property of being able to act as therapeutic cells, but the claims do *not* recite limitations requiring that the claimed composition be so used. As such, the limitations of the claim recite only the composition, which is a product of nature, and do not recite the integration of that composition into any practical application.

C. Guidance Step 2B

Finally, we evaluate whether additional elements in the claims recite "an inventive concept—i.e., an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself." *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1375 (Fed. Cir. 2015) (alteration in original) (internal quotation marks omitted). Particularly, we evaluate whether the claims include specific limitations that are not "well-understood,

routine, conventional activity previously engaged in by scientists who work in the field." *Mayo*, 566 U.S. at 79.

Appellant argues that the population of CDCs substantially depleted of CD90 positive cell subpopulation has improved potency in repair of damaged heart tissue. Appeal Br. 16 (citing Spec. Figs. 14, 17, 20–28). Appellant concludes that

> [b]ecause the recited populations of "[CDCs] substantially depleted of cells expressing the CD90 cell marker" in Claim 19 and Claim 70 provide improved results, the recited population of "[CDCs] substantially depleted of cells expressing the CD90 cell marker" are significantly more and should be subject matter eligible, contrary to the findings in the Office Action.

Id. at 16–17 (second and third alterations in original).

We are not persuaded by Appellant's argument. As discussed by the Examiner, "Appellant has not made this comparison of potency to the natural counterparts of CD90 negative cardiac progenitors found in nature." Ans. 12. Rather, "Appellant's comparisons have been made with compositions that consist of CDCs that have been depleted of CD90 expressing cells and thus are not commensurate in scope with the claimed invention." *Id.* Thus, Appellant has not demonstrated that the claimed cell population is "markedly different" than those found in nature. *Myriad*, 569 U.S. at 590–91

We therefore conclude that the claims do not amount to significantly more than a patent on the ineligible concept itself. *See Ariosa*, 788 F.3d at 1378. We therefore sustain the Examiner's rejection of claim 19 upon this ground. We sustain the Examiner's rejection of independent claim 70 for

the same reasons. Dependent claims 51, 52, 54, 59, 60, 67–69, and 71 are not argued separately, and fall with claims 19 and 70. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Rejection of claims 68 and 69 as being indefinite under 35 U.S.C. § 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph.

The Examiner rejected claim 68 as being indefinite because it is dependent on itself. Final Act. 6. Claim 69 was similarly rejected for depending from an indefinite claim. *Id.* Appellant did not argue the indefiniteness rejection of claims 68 and 69; therefore, we sustain the Examiner's rejection on this ground.

Rejection of claims 19, 51, 54, 59, 67, 70, and 71 under 35 U.S.C. § 102(b) as anticipated by Haag.

As discussed above, the Examiner finds that Haag teaches cardiac cells that are isolated from a primary culture, which are negative for CD90, depleted of more than 99% of CD90 expressing cells, and therapeutic. Final Act. 9 (citing Haag ¶¶ 10–13, 25, 30). The Examiner acknowledges that Haag does not specifically teach that the cardiac cells are derived from a cardiosphere; however, we have not been pointed to persuasive evidence on this record that distinguishes a CD90 negative cell derived from cardiac tissue and a CD90 negative cell derived from a cardiosphere. *Id.*

Appellant asserts that the Examiner erred due to an improper interpretation of the term "CDCs" as discussed above and that the Examiner failed to consider the experimental data in Kreke differentiating EDCs (explant-derived cells) from CDCs. Appeal Br. 18–19.

We are not persuaded by Appellant's arguments. As discussed above, the CDCs disclosed in Kreke are not commensurate in scope with the claims, which only include a broad process limitation rather than the specific process steps and conditions disclosed in Kreke. Although Appellant argues that the claimed CDCs are distinguishable from the cardiac derived cells of Haag, they have not persuasively shown how the claimed process step of culturing cardiospheres as an adherent monolayer culture on a solid surface of a culture vessel imparts any structural differences between the claimed CDCs and the cardiac derived cells of Haag, which are also CD90 negative. "The patentability of a product does not depend on its method of production. If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) (citation omitted).

Therefore, we sustain the Examiner's anticipation rejection of claim 19. We sustain the Examiner's anticipation rejection of independent claim 70 for the same reasons. Dependent claims 51, 54, 59, 67, and 71 are not argued separately, and fall with claims 19 and 70. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Rejection of claims 19, 51, 52, 54, 67, 70, and 71 under 35 U.S.C. § 102(b) as anticipated by Smith.

The Examiner finds that Smith teaches a composition comprising cardiospheres (CSps) that are negative for CD90. Final Act. 11. The Examiner further finds that "Smith's cardiospheres contain cardiac cells that

are derived from cardiospheres and thus contain cardiosphere-derived cells as well." *Id.*

Similar to arguments made for the other rejections, Appellant argues that *in vitro* manipulation of cardiospheres is performed to obtain CDCs and that "CDCs are a particular population of cells obtained by plating and expanding cardiospheres as an adherent monolayer culture on a solid surface of a culture vessel." Appeal Br. 19. Appellant further asserts that "a manufacturing criterion for CDCs requires that greater than 90% of the CDCs in a preparation express CD105." *Id.* at 20–22 (citing the '252 publication[8] at Figs. 2A, 5E, 18A–C, 38B–C).

We are not persuaded by Appellant's arguments. We agree with the Examiner that the evidence cited by Appellant in the '252 publication is not commensurate in scope with the claims. As found by the Examiner, "[t]he evidence is gathered from cell populations that consist of CDCs that have been formed from processes that include additional steps not claimed." Ans. 14. Appellant has not persuasively demonstrated that CDCs produced by the claimed limitation (i.e., obtained by culturing cardiospheres as an adherent monolayer culture on a solid surface of a culture vessel) have the properties discussed in the '252 publication. Furthermore, the claims do not require that the CDCs have a certain expression of CD105 or specific secretions of growth factors or growth factor receptors.

[8] Marban, US 2012/0315252, published Dec. 13, 2012 ("the '252 publication").

Accordingly, we sustain the Examiner's anticipation rejection of claim 19. We sustain the Examiner's anticipation rejection of independent claim 70 for the same reasons. Dependent claims 51, 52, 54, 67, and 71 are not argued separately, and fall with claims 19 and 70. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Rejection of claims 52 and 60 under 35 U.S.C. § 103(a) as obvious over Haag.

The Examiner finds that, with regard to claim 52, which recites "wherein said therapeutic population of cells is entirely depleted of cells expressing the CD90 marker," Haag describes cardiac derived cells that are CD90 negative and are preferably more than 99% CD90 negative. Final Act. 14 (citing Haag ¶ 25). The Examiner finds that the range of more than 99% CD90 negative includes the value of 100% negative (i.e., entirely depleted of CD90 expressing cells). *Id.*

With regard to claim 60, which recites "wherein said therapeutic population of cells is depleted of at least 90%, 95% or 99% of cells expressing the c-kit stem marker," the Examiner finds that Haag describes cardiac derived cells that are CD90 negative and preferably at least 70% negative for CD117 (c-kit). Final Act. 14 (citing Haag ¶ 30). The Examiner finds that the range of at least 70% negative includes the values of at least 90%, 95% or 99% negative for CD117 (c-kit). *Id.*

Appellant asserts that Haag fails to disclose CDCs for the reasons argued above and fails to provide motivation to produce such cells using the methods recited in the claims. Appeal Br. 23.

We are not persuaded by Appellant's arguments. For the reasons discussed above, we find that Appellant has not persuasively distinguished the claimed CDCs from the cardiac derived cells disclosed in Haag. Furthermore, as stated by the Examiner, the ranges disclosed in Haag overlap with those recited in claims 52 and 60. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness."). Therefore, we sustain the Examiner's rejection of claims 52 and 60.

Rejection of claims 19, 51, 52, 54, 59, 60, 67, 70, and 71 under 35 U.S.C. § 103(a) as obvious over Marban in view of Haag and Kisselbach.

The Examiner finds that Marban teaches "a composition comprising CDCs that are obtained by culturing cardiospheres as an adherent monolayer culture on a solid surface coated by fibronectin of a culture vessel" and that "[f]urther manipulation to form secondary cardiospheres is indicated as optional and thus not required." Final Act. 15 (citing Marban ¶ 59). The Examiner also finds that these cells are intended for use in repair of damaged heart tissue. *Id.* (citing Marban ¶ 6).

The Examiner acknowledges that Marban does not indicate that the cell composition is substantially depleted of CD90 expressing cells but finds that Haag teaches a cardiac derived cell that is negative for CD90 and also teaches that cells having this marker expression are preferred for the repair of cardiac tissue. *Id.* (citing Haag ¶¶ 10–13). The Examiner further finds that Kisselbach teaches that, when developing cell therapies, it is important to reduce fibroblast contamination. *Id.* (citing Kisselbach 31). According to

the Examiner, "[s]ince fibroblasts express CD90, removing cells that express CD90 is taught as desirable for removing contaminating fibroblasts from a cell therapy composition." *Id.* (citing Kisselbach 43).

The Examiner concludes:

> One of ordinary skill in the art would have been motivated to substantially reduce the CD90 expressing cells in the CDC composition of [Marban] because Haag and Kisslebach teach that it is desirable to remove CD90 expressing cells from a mixed cell population intended for cell therapy to remove contaminating cells. . . . One of ordinary skill in the art would have had a reasonable expectation of success because both Haag and Kisselbach describe how CD90 expressing cells can be removed.

Id. at 15–16.

Appellant asserts that Marban does not teach or suggest removing CD90 expressing cells from a cell composition intended for cardiac repair. Appeal Br. 24. With regard to Haag, Appellant asserts the same arguments as discussed above and, with respect to Kisselbach, Appellant asserts that "Kisselbach is concerned about removing contaminating fibroblasts from a homogenous cell population, and it teaches nothing about whether those CD90 positive cells in CDCs are equivalent to 'contaminating fibroblasts' among a number of different cell subpopulations comprising CDCs as a mixed cell population." *Id.* at 25. Appellant also asserts that the Examiner conducted improper hindsight reconstruction of the invention according to claims 19 and 70. *Id.*

We are not persuaded by Appellant's arguments. "Non-obviousness cannot be established by attacking references individually where the

rejection is based upon the teachings of a combination of references. [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (citation omitted). Marban discloses CDCs produced in the manner recited in the claims for repair of cardiac tissue. One of skill in the art would have looked to Haag and Kisselbach to provide motivation to remove CD90 expressing cells from the cell composition of Marban, which is intended for cell therapy (i.e., repair of cardiac tissue).

We are similarly not persuaded by Appellant's arguments regarding hindsight.

> Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper.

In re McLaughlin, 443 F.2d 1392, 1395 (CCPA 1971). We are not persuaded that the Examiner erred. Accordingly, we sustain the Examiner's obviousness rejection of claims 17 and 70. Dependent claims 51, 52, 54, 59, 60, 67, and 71 are not argued separately, and fall with claims 19 and 70. *See* 37 C.F.R. § 41.37(c)(1)(iv).

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
19, 51, 52, 54, 59, 60, 67–71	101	Eligibility	19, 51, 52, 54, 59, 60, 67–71	
68, 69	112, second paragraph	Indefiniteness	68, 69	
19, 51, 54, 59, 67, 70, 71	102(b)	Haag	19, 51, 54, 59, 67, 70, 71	
19, 51, 52, 54, 67, 70, 71	102(b)	Smith	19, 51, 52, 54, 67, 70, 71	
52, 60	103(a)	Haag	52, 60	
19, 51, 52, 54, 59, 60, 67, 70, 71	103(a)	Marban, Haag, Kisselbach	19, 51, 52, 54, 59, 60, 67, 70, 71	
Overall Outcome			19, 51, 52, 54, 59, 60, 67–71	

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED