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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/531,254	05/26/2017	Michelle Kreke	Cap15.1-PCT-US	1041

137994 7590 06/23/2020

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
06/23/2020	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MICHELLE KREKE, RACHEL SMITH, PETER HANSCOME, KIEL PECK, and AHMED IBRAHIM

Appeal 2020-000277
Application 15/531,254
Technology Center 1600

Before JEFFREY N. FREDMAN, ULRIKE W. JENKS, and JOHN G. NEW, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134(a) involving claims to stable lyophilized formulations of cardiosphere-derived cell exosomes. The examiner rejected the claims as obvious, on the ground of obviousness-type double patenting, and as reciting non-statutory subject matter. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a). Appellant identifies the real party in interest as Capricor, Inc. (Appeal Br. 3).

[2] We have considered the Specification of May 26, 2017 ("Spec."); Final Office action of Sept. 6, 2018 ("Final Act."); Appeal Brief of Mar. 6, 2019 ("Appeal Br."); Examiner's Answer of Aug. 15, 2019 ("Ans."); and Reply Brief of Oct. 15, 2019 ("Reply Br.").

Statement of the Case

Background

"The leading cause of death in the US remains heart disease . . . [with] an increasing number of heart attack survivors and disability years due to nonfatal ischemic heart disease" (Spec. 1:15–20). "Cardiosphere-derived cells (CDCs) are in clinical testing. CDCs administered after a myocardial infarction (Ml) . . . have been shown to be safe and effective in reducing scar size and increasing viable myocardium" (*id.* at 1:25–28).

"CDC-derived exosomes have been shown to recapitulate the effects of CDCs now in numerous preclinical models" (Spec. 2:1–2). Exosomes are membrane-bound vesicles . . . generated by inward budding of endosomal multivesicular bodies" (*id.* at 1:3–6). "CDCs secrete exosomes containing particular miRNAs that stimulate cardiomyocyte proliferation, spur angiogenesis, and improve functional recovery in Ml models" (*id.* at 2:4–6). "It was found that miR-201 and miR-146a were up-regulated in CDC exosomes in comparison to NHDF (normal human dermal fibroblast) exosomes" (*id.* at 3:6–8).

The Specification states "[t]here is a need in the art for better exosome formulations, particularly for clinical use, and that are stable" (Spec. 3:24–25).

The Claims

Claims 1–15 are on appeal. Because Appellant does not argue the claims separately, we focus our analysis on claim 1, and claims 2–15 stand or fall with that claim. 37 C.F.R. § 41.37 (c)(1)(iv). Claim 1 reads as follows:

> 1. A stable dry lyophilized exosome formulation suitable for administration to a human comprising at least 10^6 exosomes, wherein, upon rehydration, the lyophilized exosomes maintain at least 90% of the levels of miR-210 and miR-146a of the exosome formulation pre-lyophilization, and wherein the exosome formulation is generated from cardiosphere-derived cells (CDCs).

The Issues

A. The Examiner rejected claims 1–15 as unpatentable under 35 U.S.C. § 101 as directed to non-statutory subject matter (Final Act. 6–8).

B. The Examiner rejected claims 1–15 as unpatentable under 35 U.S.C. § 103 as obvious over Ibrahim,[3] Mitsialis,[4] Vrijsen,[5] and Chang[6] (Final Act. 10–11).

C. The Examiner rejected claims 1–15 as unpatentable on the ground of obviousness-type double patenting over claims 1–3 and 9–17 of U.S. Patent 9,828,603 in view of Chen, Mitsialis, and Chang[7] (Final Act. 3–4).

D. The Examiner rejected claims 1–15 as unpatentable on the ground of obviousness-type double patenting over claims 12–17 of copending application 15/790,962 (now US 10,457,942, issued Oct. 29, 2019) in view

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[3] Ibrahim, et al, *MicroRNA-Containing Exosomes from Cardiosphere-Derived Cells Stimulate Cardiomyocyte Proliferation and Angiogenesis in vitro, and Improve Functional Recovery after Myocardial Infarction in Mice*, 126 Circulation Res. Suppl. 21, Abstract 14697 (2012).
[4] Mitsialis et al., US 2014/0065240 A1, published Mar. 6, 2014.
[5] Vrijsen et al, *Cardiomyocyte Progenitor Cell-Derived Exosomes Stimulate Migration of Endothelial Cells*, 14(5) J. Cell. Mol. Med. 1064–70 (2010).
[6] Chang et al, U.S. 2005/0002998 A1, published Jan. 6, 2005.
[7] Chen, et al, *Cardiac Progenitor-Derived Exosomes Protect Ischemic Myocardium from Acute Ischemia/Reperfusion Injury*, 431 Biochem. Biophys. Res. Comm. 566–71 (2013).

of Chen, Mitsialis, and Chang (Final Act. 5–6).

A. 35 U.S.C. § 101

The Examiner finds that claim 1 is "directed to a preparation of exosomes obtained from CDCs, wherein the exosomes comprise miR-210 and miR-146a" (Final Act. 7).

The Examiner cites references to establish that the human heart comprises resident CDCs[8] (Final Act. 7). The Examiner finds

> no evidence of record demonstrating that the claimed exosomes are any different from naturally occurring exosomes derived from the resident CDCs nor is there any evidence of record demonstrating that lyophilization (process routinely used in the prior art) results in a composition which is markedly different from the naturally occurring counterparts.

(*id.*).

Appellant contends "cardiospheres and CDCs are *in vitro* products without a natural counterpart, and exosomes generated therefrom also must be recognized as an *in vitro* product without a natural counterpart" (Appeal Br. 8).

The Alice Test

The Supreme Court has long interpreted 35 U.S.C. § 101 to include implicit exceptions: "[l]aws of nature, natural phenomena, and abstract

[8] Liang, et al, *Migration of Resident Cardiac Stem Cells in Myocardial Infarction*, 296 Anatom. Rec. 184–91 (2013); Li, et al, *Cardiospheres Recapitulate a Niche-Like Microenvironment Rich in Stemness and Cell-Matrix Interactions, Rationalizing Their Enhanced Functional Potency for Myocardial Repair*, 28 Stem Cells 2088–98 (2010); Koudstaal, et al, *Concise Review: Heart Regeneration and the Role of Cardiac Stem Cells*, 2 Stem Cells Transl. Med. 434–43 (2013).

ideas" are not patentable. *See, e.g.*, *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014).

In determining whether a claim falls within an excluded category, we are guided by the Supreme Court's two-step framework, described in *Mayo* and *Alice*. *Id.* at 217–18 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 75–77 (2012)). In accordance with that framework, we first determine if there is a judicial exception. Although composition of matter claims are generally eligible subject matter, claims that are directed only to laws of nature and/or natural phenomena are directed to patent ineligible concepts. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376 (Fed. Cir. 2015).

If the claim is "directed to" a judicial exception, we turn to the second step of the *Alice* and *Mayo* framework, where "we must examine the elements of the claim to determine whether it contains an 'inventive concept' sufficient to 'transform' the claimed abstract idea into a patent eligible application." *Alice*, 573 U.S. at 221 (quotation marks omitted).

2019 Guidance

The United States Patent and Trademark Office published guidance on the application of 35 U.S.C. § 101. USPTO's *2019 Revised Patent Subject Matter Eligibility Guidance* ("Guidance").[9] Under the Guidance, in determining what concept the claim is "directed to," we first look to whether the claim recites:

> (1) any judicial exceptions, including "[l]aws of nature, natural phenomena, and abstract ideas," (quoting *Alice*, 573 U.S. at 216) and/or including certain groupings of abstract ideas

[9] *2019 Revised Patent Subject Matter Eligibility Guidance*, 84 Fed. Reg. 50 (January 7, 2019).

> (i.e., mathematical concepts, certain methods of organizing human activity such as a fundamental economic practice, or mental processes) (Guidance Step 2A, Prong 1); and
>
> (2) additional elements that integrate the judicial exception into a practical application (*see* MPEP § 2106.05(a)–(c), (e)–(h)) (Guidance Step 2A, Prong 2).

Only if a claim (1) recites a judicial exception and (2) does not integrate that exception into a practical application, do we then look to whether the claim contains an "'inventive concept' sufficient to 'transform'" the claimed judicial exception into a patent-eligible application of the judicial exception. *Alice*, 573 U.S. at 221 (quoting *Mayo*, 566 U.S. at 82).

In so doing, we thus consider whether the claim:

> (3) adds a specific limitation beyond the judicial exception that are not "well-understood, routine and conventional in the field" (*see* MPEP § 2106.05(d)); or
>
> (4) simply appends well-understood, routine, conventional activities previously known to the industry, specified at a high level of generality, to the judicial exception.

(Guidance Step 2B). *See* Guidance, 84 Fed. Reg. at 54–56.

Analysis

Appellant's claims recite patent-eligible subject matter. Because the same issues are present in each of the claims, we focus our consideration on representative claim 1. The same analysis applied below to claim 1 also applies to the other rejected claims.

A. Guidance Step 1

We first consider whether the claimed subject matter falls within the four statutory categories set forth in § 101, namely "[p]rocess, machine, manufacture, or composition of matter." Guidance, 84 Fed. Reg. at 53–54;

see 35 U.S.C. § 101. Claim 1 recites a "formulation" and, thus, falls squarely within the "composition of matter" category. Consequently, we proceed to the next steps of the analysis.

B. Guidance Step 2A, Prong 1

The Revised Guidance instructs us first to determine whether any judicial exception to patent eligibility is recited in the claim. The Revised Guidance identifies products of nature as having been identified by the courts as judicial exceptions. 84 Fed. Reg. at 54. We therefore first look to see if the claim recites any judicial exceptions.

The Examiner, as noted above, finds that CDC-derived exosomes are products of nature, specifically the result of a series of steps giving rise to a preferential enrichment of a particular naturally-occurring cell type. (Final Act. 7–8; Ans. 12). Appellant, however, contends that the evidence does not support a finding that the claimed exosomes are naturally occurring (Appeal Br. 8–9). Appellant contends

> cardiosphere-derived cells (CDCs) and exosomes generated therefrom are produced by a series of *in vitro* manipulations that begin with processing a donor cardiac tissue specimen (e.g., biopsy) into a plurality of tissue explants, which are then cultured until cells migrate from the explant, collecting the cells that migrate from the explant, thereby generating explant-derived cells (EDCs).

(Appeal Br. 5; *cf*. Spec. 17:25 to 18:24).

"[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). The initial burden of demonstrating that exosomes obtained from CDCs are naturally occurring

therefore rests upon the Examiner, and only if that burden is met, does Appellant then have the burden of rebutting the Examiner's position.

Examiner's cited art

The Examiner finds "[i]t is well-known that human heart comprises a heterogeneous population of resident CDCs capable of forming cardiospheres in culture" (Ans. 6; citing Liang,[10] Li,[11] Koudstaal[12]). The Examiner also finds that "[i]t is also well-known in the art that exosomes are naturally secreted by cells in vivo where they are involved in intercellular communication between different cell types" (Ans. 7, citing Vrijsen).

We are not persuaded that the cited references support the Examiner's position that cardiospheres are not markedly different from naturally occurring cells in the human heart. Liang teaches that:

> Several different types of CSCs have so far been isolated and expanded by several groups . . . There is partial overlap in marker expression but the origins and exact lineage relationships among these various CSC populations are still not clear. It remains to be determined whether some or all of these cells originate from a common stem cell population and are simply at different stages of development in the heart, or whether they are independent cell lineages derived from distinct stem/progenitor cell populations.

(Liang 186, col. 1). Thus, Liang does not clearly demonstrate that CSC populations are identical to naturally occurring cells.

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[10] Liang et al., *Migration of Resident Cardiac Stem Cells in Myocardial Infarction*, 296 The Anatomical Record 184–91 (2013).
[11] Li et al., *Cardiospheres Recapitulate a Niche-Like Microenvironment Rich in Stemness and Cell-Matrix Interactions, Rationalizing Their Enhanced Functional Potency for Myocardial Repair*, 28 Stem Cells 2088–98 (2010).
[12] Koudstaal et al., *Concise Review: Heart Regeneration and the Role of Cardiac Stem Cells*, 2 Stem Cells Translational Medicine 434–43 (2013).

Li teaches "expression profile of ECM and adhesion molecule genes was analyzed using pathway-focused PCR arrays . . . Twelve of these mRNAs were increased more than fourfold after 3 days of 3D cardiosphere culture" (Li 2092, col. 1–2). Li teaches "enhanced expression levels of integrin-α2 and laminin-β1 in cardiospheres disappear in the dissociated cells, falling to levels comparable with those in monolayer-cultured cells" Li 2095, col. 1). Thus, Li provides evidence that cardiospheres express different genes during culture, differ from dissociated cells, and therefore suggests that cardiospheres markedly differ from naturally occurring cells.

Table 1 of Koudstaal is reproduced below:

Table 1. Resident stem/progenitor cells in the mammalian heart

CSC type	Isolation marker	Stem cell molecular markers		Species	Fetal/ neonatal	Adult	Stemness criteria [55]			Cardiac myocyte formation in vitro	Description	References
		Positive	Negative				Multipotent	Self-renewal	Clonogenic			
c-kit	c-kit	c-kit, Sca-1, MDR-1, CD90	CD34, CD45	Mouse, rat, dog, pig, human	Yes	Yes	Yes	Yes	Yes	Yes	Cocultured with neonatal rat cardiomyocytes	[12, 52, 53, 67]
CMPC	Sca-1	Sca-1, c-kit, CD105, CD31 CD90	CD14, CD34, CD45	Mouse, human[a]	Yes	Yes	Yes	Yes	Yes	Yes	Differentiation protocol based on TGF-β/5′-AZA	[33, 36, 54]
CDC	None[b]	c-kit, CD105, Sca-1, CD90, CD34, CD31	MDR-1, CD133, CD45	Mouse, rat, pig, human	Yes	Yes	Yes	Yes	Yes	Yes	Cocultured with rat cardiomyocytes	[46, 49, 50, 68]
SP cells	Abcg2[c]	Abcg2, Sca-1, MDR-1, CD133	CD31, CD34, CD45, c-kit	Mouse, rat	Yes	Yes	Yes	Yes	No	Yes	Cocultured with mouse cardio-myocytes	[32, 40–43]
Isl-1	Islet-1	Islet-1	Sca-1, c-kit, CD31	Mouse, rat, human	Yes	No	Yes	Yes	Yes	Yes	Cocultured with neonatal mouse cardiomyocytes	[37–39]

[a]Note: Sca-1 does not exist in humans; the antibody against Sca-1 binds to an unknown Sca-1-like antigen.
[b]Isolation based on enzymatically digested single cell suspension of myocardial biopsies. After several days in culture, loosely adherent cardiospheres are formed that can be separated from fibroblast-like cells attached to the fibronectin-coated culture dish [50].
[c]Isolation based on fluorescence activated cell sorting analysis selecting for the G-member protein $Abcg2^{pos}$ cells that are able to efflux Hoechst dye [32].
Abbreviations: 5′-AZA, 5′-azacytadine; CDC, cardiosphere-derived cell; CMPC, cardiomyocyte progenitor cell; CSC, cardiac stem cell; Isl-1, transcription factor Islet-1; SP, side population; TGF, transforming growth factor.

Table 1 depicts a "schematic overview of resident stem/progenitor cells in the mammalian heart" (Koudstaal 436, 438). Table 1 of Koudstaal teaches that cardiosphere-derived cells (CDC) lack any isolation marker and differ from known types of cardiac stem cells which have particular isolation markers and which are not CD34 positive and MDR-1 negative (*see* Koudstaal 438). Thus, the evidence in Koudstaal does not demonstrate that cardiosphere-derived cells are naturally occurring.

Vrijsen does not directly address the status of cardiosphere-derived cells, rather focusing on cardiomyotcyte progenitor cells, and do not discuss the impact of culture on such cells (*see* Vrijsen 1065, col. 1).

Ibrahim Declaration[13]

The Specification teaches the process by which exosomes were prepared:

> Immediately upon receipt, hearts were grossly dissected and cut into biopsy-sized pieces . . . referred to as explants . . . In order to generate allogeneic CDCs, explants were plated on CELLBIND® CellSTACK® vessels (Corning Life Sciences). After 1-2 weeks, cellular outgrowth emerging from the explants became confluent. These explant derived cells (EDCs) were harvested using IX TrypLE™ (lnvitrogen). EDCs were either cryopreserved as the master cell bank (MCB), and then cultured as cardiospheres (CSps), or placed immediately into CSp culture conditions. . . . Allogeneic CDCs were grown by seeding CSps on fibronectin-coated Nunc* TripleFlasks (Thermo Scientific), and passaging when confluent. CDCs at varying passage number were seeded on to fibronectin-coated Cell Bind cellstacks and allowed to become confluent for exosome production. . . . Exosomes were filtered using a 0.45 μm to remove cellular debris and then isolated by ultrafiltration.

(Spec. 17:27 to 18:20).

The Ibrahim Declaration "performed experiments to measure exosome microRNA contents, including miR-146a, and compared exosomes derived from explant cells, EDCs and CDCs, with each of the aforementioned explant cells, EDCs and CDCs being derived from the same donor" (Ibrahim Decl. 3). The Ibrahim Declaration compared "exosome microRNA contents across explant cell-, EDC- and CDC-derived exosomes" (Ibrahim Decl. ¶ 4). Figures 1 and 2 of the Ibrahim Declaration are reproduced below:

[13] Declaration of Dr. Ahmed Ibrahim, dated Feb. 24, 2017 in US Application 14/421,355.

Figure 1

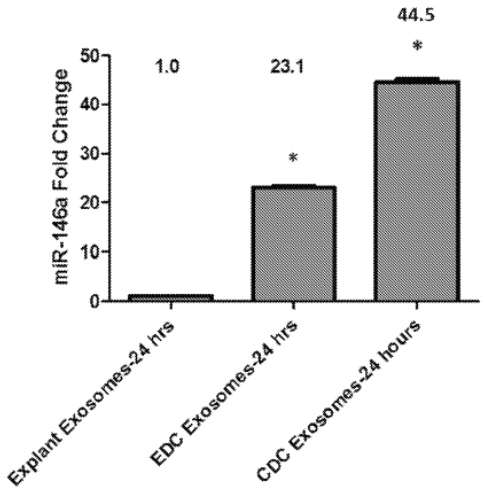
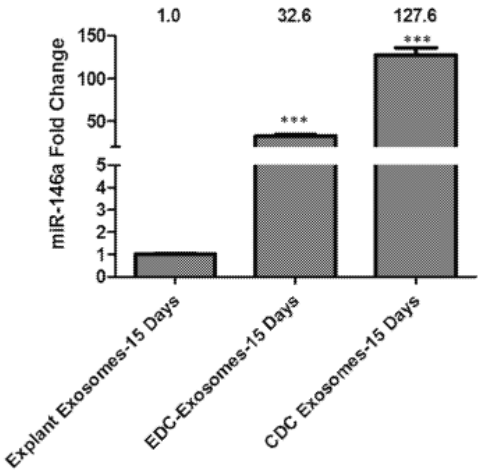


Figure 2



Figures 1 and 2 of the Ibrahim Declaration show comparisons "of miR-146a levels in exosomes isolated from the conditions media of explants, Explant-derived Cells (EDCs), and cardiosphere-derived cells (CDCs)" harvested at 24 hours and 15 days of conditioning, respectively (Ibrahim Decl. 4–5). Based on this data, Dr. Ibrahim concludes "CDCs-derived exosomes are different from explant cell-, EDC-derived exosomes" (Ibrahim Decl. ¶ 8).

The Examiner responds that "the observed increase in the miR-146a and miR-22 levels from explant to EDCs and from EDCs to CDCs reflects an enrichment in cells (i.e., CDCs) secreting exosomes naturally comprising higher miR-146a and miR-22 levels as opposed to exosomes secreted from the other cell types" (Ans. 12). The Examiner contends the final cell population with higher miR-146a levels is due to enrichment "**and not** changes in the phenotype following isolation and cultivation for 15 days" (Ans. 14).

However, the Examiner provides no rebuttal evidence, as opposed to argument, demonstrating that the increased miR-146a levels result solely

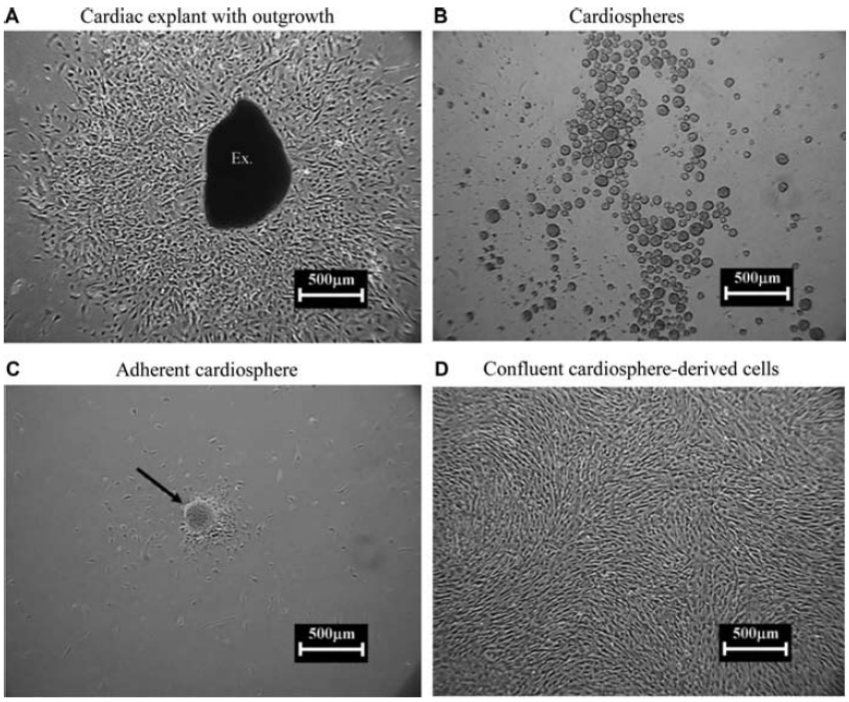
from enrichment of naturally occurring cells, and not changes that occur during *in vitro* isolation and culture of the cells for several weeks.

Appellant's cited art

Appellant cites White[14] and Davis[15] to support the position "cardiospheres and CDCs are in vitro products without a natural counterpart, and exosomes generated therefrom also must be recognized as an in vitro product without a natural counterpart" (Appeal Br. 8).

The Examiner responds "White et al. and Davis et al. teach that EDCs are heterogeneous and include a subpopulation of cardiosphere forming cells from which CDCs are derived" (Ans. 19).

Figure 1 of White is reproduced below:



[14] White et al., *Intrinsic Cardiac Origin of Human Cardiosphere-Derived Cells*, 34 European Heart Journal 68–75 (2013).
[15] Davis et al., *Validation of the Cardiosphere Method to Culture Cardiac Progenitor Cells from Myocardial Tissue*, 4(9) PLoS ONE, 2009 e7195 1–8 (2009).

> Figure 1 Representative cell morphology during each stage of the cardiosphere-derived cell protocol. (A) A cardiac biopsy explant (Ex.), with outgrowth of a monolayer of cells on fibronectin coated plastic. (B) The monolayer is harvested and placed into poly-D-lysine-coated plastic wells, resulting in the formation of floating clusters of cells known as cardiospheres. (C) The cardiospheres are plated back onto fibronectin-coated plastic, whereupon they adhere, flatten and spread once again as a monolayer (cardiosphere-derived cells). Black arrow indicates one cardiosphere. (D) Sheets of cardiosphere-derived cells become confluent. They are then harvested and passaged.

(White 71).

Davis teaches, with respect to cardiospheres, that "core cells have a cardiac progenitor immunophenotype dominated by the expression of stem cell and cardiomyocyte-related antigens. Peripheral cells represent ***spontaneous differentiation*** of precursor cells into endothelial, mesenchymal, or cardiomyogenic lineages, and/or the encapsulation of core progenitors by a subset of supportive cardiac mesenchymal cells" (Davis 5, col. 1–2; emphasis added). Davis further explains that "when CPCs are cultured directly from myocardial tissue by carefully-established methods, further sub-culture permits the formation of self-organizing cardiospheres that create a complex, niche-like environment" (Davis 5, col. 2). Thus, Davis explains that the explant cells undergo changes in expression and differentiation from cells naturally found in the heart (*see id.*).

White teaches that the morphology of cardiospheres differs from that of naturally occurring heart cells, supporting the position that the cells have altered in culture (*see* White 71). Davis expressly states that the cells are differentiated and therefore differ from naturally occurring heart cells, and

form cardiospheres that show different morphology than naturally occurring heart cells (*see* Davis 5).

Therefore, a preponderance of the evidence supports Appellant's position that the cells recited in claim 1 are not naturally occurring and markedly different than naturally occurring heart cells. None of the Examiner's cited prior art demonstrates that the CPCs are naturally occurring as discussed above. The Ibrahim Declaration demonstrates a marked difference in the expression of each of miR-146a and miR-22 in exosomes obtained from CDCs compared to each of explant and explant-derived cell exosomes (*cf.* Appeal Br. 8–9). Appellant's cited art suggests that cardiospheres are composed of cells that have undergone changes from naturally occurring cells and thereby are markedly different from naturally occurring cells.

In the instant case, the evidence discussed above does not establish that the claimed exosome formulation of cardiosphere-derived cells is itself necessarily naturally occurring, or that the cells themselves are necessarily naturally occurring.

Accordingly, under Guidance Step 2A, Prong 1, we conclude that the composition of claim 1 has not been shown to be a product of nature, and thus is not directed to a patent ineligible judicial exception. Consequently, our analysis ends here.

Conclusion of Law

A preponderance of the evidence of record supports the conclusion that claims 1–15 are directed to patent eligible subject matter.

B. 35 U.S.C. § 103 over Ibrahim, Mitsialis, Vrijsen, and Chang.

The Examiner finds Ibrahim teaches "a liquid exosome preparation generated from human CDCs, wherein the exosomes comprise high amounts of miR-210 and miR-146a" (Final Act. 11). The Examiner acknowledges that Ibrahim does "not specifically teach at least 10^6 or at least 10^8 exosomes" but finds it "obvious to vary the amount of exosomes in the preparation to optimize the preparation for therapeutic purposes" (*id.*).

The Examiner also acknowledges that Ibrahim does "not teach stabilizing and preserving activity via lyophilization" (Final Act. 12). The Examiner finds Mitsialis teaches "exosomes can be lyophilized" (*id.*).

The Examiner finds Vrijsen teaches that, like liposomes, "exosomes are lipid bilayer vesicles . . . comprising proteins and nucleic acids" (Final Act. 12). The Examiner finds that Chang evidences that "lyophilizing liposomes comprising proteins, and nucleic acids results in stable compositions which maintain at least 90% of biological activity upon reconstitution" (*id.*) The Examiner finds it would have been obvious to combine the teachings of Ibrahim, Mitsialis, Vrijsen, and Chang "to achieve the predictable result of obtaining a stable [exosome] composition suitable for prolonged storage and maintaining at least 90% of its biological activity upon rehydration" (*id.*).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the combination of Ibrahim, Mitsialis, Vrijsen, and Chang renders the claims obvious?

Principle of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Findings of Fact

1. Ibrahim teaches "[e]xosomes are rich in microRNAs (mirs) which may function in a paracrine fashion. Cardiosphere-derived cells (CDCs) have been shown to regenerate heart after myocardial infarction (MI) in animal models and in the CADUCEUS clinical trial" (Ibrahim, abstract).

2. Ibrahim teaches "mice injected with exosomes from CDCs during acute MI showed higher LVEF at two weeks . . . and four weeks . . . as well as increased regeneration of the infarcted myocardium" (Ibrahim, abstract).

3. Ibrahim teaches: "Mir microarray analysis identified mir-146a, mir 22, mir 24, and mir 210 among the most highly-upregulated mirs in CDC-exosomes compared to NHDF" (Ibrahim, abstract). Ibrahim concludes: "Mir-containing exosomes secreted by CDCs exhibit multiple beneficial effects on injured myocardium, suggesting that exosomes may mediate some of the therapeutic effects of CDCs" (Ibrahim, abstract).

4. Mitsialis teaches "exosomes may be used (e.g., administered) in pharmaceutically acceptable preparations" and teaches:

> The preparations of the invention are administered in effective amounts. An effective amount is that amount of an agent that alone stimulates the desired outcome. The absolute amount will depend upon a variety of factors, including the material selected for administration, whether the administration is in single or multiple doses, and individual patient parameters including age, physical condition, size, weight, and the stage of the disease. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation.

(Mitsialis ¶¶ 85, 93).

5. Mitsialis teaches "the exosomes may be in lyophilized or other powder or solid form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use" (Mitsialis ¶ 97).

6. Vrijsen teaches: "Exosomes are small membrane vesicles with a lipid bilayer" (Vrijsen 1066, col. 1).

7. Chang teaches "a method of preparing a stable complex comprising a ligand and a cationic liposome encapsulating a therapeutic or diagnostic agent" (Chang ¶ 2).

8. Chang teaches a "method for preparing a stable complex comprising a ligand and a cationic liposome . . . [by] combining a complex comprising a ligand and a cationic liposome . . . and lyophilizing the resultant solution of complex and sucrose to obtain a lyophilized preparation" (Chang ¶¶ 11–13).

9. Chang teaches "the preparation retains at least about 85% of its pre-lyophilization activity, and more preferably, at least about 90% of its prelyophilization activity" (Chang ¶ 15).

10. Chang teaches the "lyophilized preparation is stable within a range of from about 2-8° C. to about -80° C. for a period of at least 6 months without losing significant activity" (Chang ¶ 27). Chang further explains "[t]hese studies indicate that lyophilization of the complete complex is feasible and that previous difficulties with stability and shelf life . . . can be overcome" (Chang ¶ 78).

Analysis

We adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Final Act. 10–13; FF 1–10) and agree that the claims are obvious over Ibrahim, Mitsialis, Vrijsen, and Chang. We

address Appellant's arguments below.

Appellant contends that because "there is no indication in Mitsialis *et al.* that lyophilization of exosomes was ever performed or that it could result in a stable dry lyophilized exosome formulation . . . Mitsialis *et al.* cannot provide any expectation of success in achieving the claimed invention" (Appeal Br. 10–11). Appellant further contends that "Mitsialis et al. only pertains to compositions comprising mesenchymal stem cell (MSC) derived exosomes, whereas the claimed invention pertains to exosomes derived from CDCs" and argues the "impropriety of such an overbroad approach" (*id.* at 11).

We find these arguments unpersuasive. The Examiner reasonably asserts that lyophilization of one type of exosome, as taught by Mitsialis, would have had a reasonable expectation of success when applied to a different type of exosome (FF 5). Mitsialis is a published US patent application and as such, "is presumptively enabling barring any showing to the contrary by a patent applicant." *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012). No such showing has been made by Appellant.

Moreover, "[o]bviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009). While Mitsialis alone provides a reasonable expectation of success, that expectation is enhanced by the express disclosure of Chang. Chang teaches that liposomes, composed of a lipid bilayer containing nucleic acids and studded with proteins, can be successfully lyophilized with retention of 90% activity (FF 7–10). Because the exosomes of Ibrahim are also composed of lipid bilayers containing nucleic acids and studded with proteins, the ordinary artisan

would have found it reasonable to expect that substituting Ibrahim's exosomes for liposomes in the lyophilization method of Chang (FF 1–3, 7–10), as suggested by Mitsialis for exosomes (FF 5), would have had a reasonable expectation of success. Appellant provides no evidence to the contrary.

As to the issue of an "overbroad" approach, "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 550 U.S. at 417. Appellant provides no persuasive reasoning or evidence explaining why using well-known storage methods like lyophilization for Ibrahim's exosomes would not have obtained the expected result shown by Chang (FF 1–3, 7–10).

Appellant contends "Vrijsen et al. does not teach lyophilizing exosomes, and Chang et al. pertains to liposomes, not exosomes. Further, Vrijsen et al. teaches using ***foetal*** heart tissue and using ***mouse*** anti-Sea-I coated magnetic beads to ***isolate and/or purify*** cardiomyocyte progenitor cells" (Appeal Br. 12). Appellant contends "CDCs, unlike the cells of Vrijsen et al., are an unsorted mixed population of cells, and CDCs comprise a mixed population of cells having fixed ***collective*** properties, as evidenced by White *et al.* and Davis *et al.*" (*id.* at 14).

We find Appellant's argument unpersuasive because it fails to recognize that the rejection is based on the combination of references, not any single reference alone. *In re Keller*, 642 F.2d 413, 425 (CCPA 1981) ("The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in

any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art."). Here, Ibrahim teaches the exosome composition of interest for treatment of patients with myocardial infarction (FF 1–3), but does not teach storage of these exosomes. Mitsialis and Chang teach that lyophilization may be used to store exosomes and liposomes, respectively, where exosomes are a naturally occurring type of liposome[16] (FF 4, 5, 7–10) as demonstrated by Vrijsen (FF 6).

Conclusion of Law

The evidence of record supports the Examiner's conclusion that the combination of Ibrahim, Mitsialis, Vrijsen, and Chang renders the claims obvious.

C. & D. Double Patenting

Appellant advances the same argument concerning the double patenting rejections made by the Examiner over each of the claims of the 9,828,603 patent, and the claims of 15/790,962 application (now US 10,457,942), both in view of Chen, Mitsialis, and Chang. Because the same issue is dispositive for both rejections, they will be addressed together.

Appellant argues "for the same reasons as presented above with respect to the rejections under 35 U.S.C. §§ 101 and 103, the cited claims and references provide no reasonable expectation of success." (Appeal Br. 14; *cf. id*. at 16).

[16] *See, e.g.*, https://medical-dictionary.thefreedictionary.com/liposome, which defines "liposome" as "a microscopic spherical particle formed by a lipid bilayer enclosing an aqueous compartment." (Accessed June 16, 2020).

Because we do not find Appellant's arguments persuasive with regard to the obviousness rejection over Ibrahim, Mitsialis, Vrijsen, and Chang as discussed above, we similarly are not persuaded by Appellant's arguments regarding the double patenting rejection, which relies on substantially the same art. We adopt the reasoning and arguments of the Examiner (*see* Final Act. 3–6) and affirm these two rejections.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–15	101			1–15
1–15	103	Ibrahim, Mitsialis, Vrijsen, Chang	1–15	
1–15	Obviousness-type Double Patenting	US 9,828,603, Chen, Mitsialis, Chang	1–15	
1–15	Obviousness-type Double Patenting	US 14/958,784, Chen, Mitsialis, Chang	1–15	
Overall Outcome			1–15	

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

AFFIRMED