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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte BALAJI SITHARAMAN and BHAVNA S. PARATALA

Appeal 2019-003437
Application 15/644,172
Technology Center 1600

Before FRANCISCO C. PRATS, RAE LYNN P. GUEST, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellant[1] seeks our review, under 35 U.S.C. § 134(a), of the Examiner's decision to reject claims 47, 48, 50–53, and 66. (Appeal Brief filed October 16, 2018 ("Appeal Br.") 1.) We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM-IN-PART.

Appellant's Specification is directed to magnetic graphene-like nano- and microparticles that serve as contrast agents ("CAs") in magnetic

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[1] We use the word "Appellant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party-in-interest as The Research Foundation for the State University of New York. (Appeal Br. 2.)

resonance imaging ("MRI"). (*See* Specification ("Spec.") ¶ 2.) According to the Specification, CAs improve detection of pathologic lesions by increasing sensitivity and diagnostic confidence. (*See id.* at ¶ 3.) CAs are reported to work by accelerating the process of relaxing water protons, or accelerating "relaxivity." (*See id.* at ¶ 4.) The effectiveness of a CA can be evaluated by measuring relaxivity, which is the change in relaxation rate (the inverse of relaxation time) per unit of CA concentration. (*See id.* at ¶ 4.)

Appellant reports that there are two main types of CAs: T1 MRI CAs, which decrease longitudinal T1 relaxation times of water protons, and T2 MRI CAs, which decrease transverse T2 relaxation times of water protons. (*See id.*) Appellant reports that many clinical MRI CAs are lanthanoid element gadolinium (Gd) ion-based T1 CAs and that the inner-transitional element manganese (Mn) is known as a possible alternative to gadolinium. (*See id.* at ¶¶ 5–6.)

Previously, carbon nanostructures, such as gadofullerenes and gadonanotubes, which encapsulate Gd^{+3} metal ion, have been proposed as T1 CAs for MRI and some Gd^{3+} ion carbon nanostructures have increased relaxivity. (*See id.* at ¶ 7.) According to Appellant, the efficacy of Mn^{2+} ion carbon nanostructure complexes as MRI CAs has not been investigated previously. (*See id.*)

Appellant reports that they have invented MRI CAs comprising trace amounts of Mn^{+2} ions intercalated within graphene sheets and that the relaxivity of these compositions is increased up to two orders compared to paramagnetic chelate compounds. (*See id.* at ¶ 9.) Appellant reports further that intercalation within graphene sheets, not the size shape, or architecture

of the particles, is the key determinant for increasing relaxivity. (*See id.* at ¶¶ 117 and 134.)

The Examiner rejected Appellant's claims 47, 48, 50–53, and 66 under 35 U.S.C. § 103(a) as being unpatentable over Sarmeo[2], Lee[3], Wang[4], and Dai[5]. (*See* Final Office Action issued June 20, 2018 ("Final Act.") 3–7.) We review independent claims 47 and 66 separately.

Claim 66

Appellant's claim 66 recites:

> A composition for use with magnetic resonance imaging, comprising:
> (i) a sufficient amount of the magnetic composition comprising a magnetic metal intercalated in an oxidized graphene nanostructure or a graphitic nano- or microstructure, wherein said magnetic metal comprises Mn, wherein a concentration of Mn in the magnetic composition is between 0.27 ppm and 1.48 ppm; and
> (ii) one or more physiologically acceptable carriers or excipients.

(Appeal Br. 11.)

We agree with the Examiner's finding that Sarmeo teaches the intercalation of manganese chloride into graphite carbon fibers. (*See*

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[2] Sarmeo et al. "Intercalation of manganese chloride into mesophase pitch-based graphite fibers via gaseous complexes," 39 CARBON 2049–58 (2001).
[3] Lee et al., "Multifunctional Metal-Graphite Nanocrystals," U.S. Patent Application Publication 2008/0213189Al, published September 4, 2008.
[4] Wang et al., "Mn_30_4 nanoparticles embedded into graphene nanosheets: Preparation, characterization, and electrochemical properties for supercapacitors," 55 ELECTROCHIMICA ACTA 6812–17 (2010).
[5] Dai et al., "Supramolecular Functionalization of Graphitic Nanoparticles for Drug Delivery," U.S. Patent Application Publication 2009/0087493 Al, published April 2, 2009.

Examiner's Answer issued January 17, 2019 ("Ans.") 3, citing Sarmeo abstract, 2052, 2053.) Sarmeo does not teach including a physiologically acceptable carrier or excipient or that the manganese chloride intercalated graphite carbon fibers can be used in MRI. (*See* Ans. 3.) We agree with the Examiner that Lee teaches magnetic nanocrystal compositions comprising metals or metal alloys and graphene-like nanostructure for use *in vivo* as MRI contrast agents. (*See* Ans. 3–4, citing Lee abstract.) We also agree that Lee teaches that the magnetic nanocrystals can comprise manganese, for example $MnFe_2O_4$. (*See* Ans. 4, citing Lee ¶ 54.) In addition, as the Examiner finds, Lee teaches that CAs were known to be diluted in 5% dextrose solution. (*See* Ans. 4, citing Lee ¶¶ 42, 131, and claim 34.)

The Examiner determines that it would have been obvious for one of ordinary skill in the art to use the fibers of Sarmeo for MRI and to administer them with a pharmaceutically acceptable carrier because Lee teaches that MRI CAs can include graphene compositions intercalated with Mn. (*See* Ans. 4.) The Examiner also finds that it would have been obvious to optimize the amount of Mn in the composition based on *In re Aller*, 220 F.2d 454, 456 (CCPA 1955), which explains that "[n]ormally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification."

Appellant argues that the Examiner fails to explain why it would have been obvious to optimize the concentration of Mn to arrive the composition recited in claim 66. (*See* Appeal Br. 7–8.) Appellant cites *In re Stepan,* 868 F.3d 1342, 1346 (Fed. Cir. 2017), for the determination that "[a]bsent some additional reasoning, the Board's finding that a skilled artisan would have

arrived at the claimed invention through routine optimization is insufficient to support a conclusion of obviousness."

We disagree. The Examiner's reasoning that Lee teaches additional metals may be present across the entire range of ratios to iron in nanocrystals for MRI CAs is persuasive. (*See* Ans. 4–5, citing Lee ¶ 35 ("The Fe to other metal (e.g., Co) ratio may be between 0:100 to 100:0.").) Lee teaches that $MnFe_2O_4$ is one such MRI CA. (*See* Lee ¶ 54.) Thus, the teachings of Lee evince that the skilled artisan would have known that different amounts of Mn in metal graphite MRI CA compositions would have been obvious.

Furthermore, Lee teaches that when formulating CAs for *in vivo* use, the dosage "may be determined through routine experimentation, and may be expected to be about 0.01 to 100 μM of metal/Ge per kilogram of body weight, that is diluted in about 100 mL of 5% dextrose solution . . . ." (Lee ¶ 131; *see* Ans. 4.) Thus, Lee teaches that the amount of metal required for *in vivo* imaging is a result effective variable that can be determined through routine optimization.

Appellant argues further that the Examiner fails to show there would have been a reasonable expectation of success in achieving the claimed Mn concentration range recited in claim 66. (*See* Appeal Br. 8.) Because Lee teaches that a wide range of ratios of additional metal in relation to Fe would work and teaches that the amount of metal may be determined through routine optimization, we are not persuaded that the Examiner erred in rejecting claim 66 as being obvious over the prior art.

Appellant's arguments regarding the Board's decision in *Ex parte Conti*, App. No. 2011-010982 (PTAB March 28, 2013) are unpersuasive and irrelevant. The claims in that case were directed to different subject matter

(^{18}F-labeled nucleotide analogues), the cited prior art was different, and different issues were raised (substitution of analogues in PET imaging compositions). (*See* Appeal Br. 8.)

We note that Appellant does not argue in the Appeal Brief that the composition recited in claim 66 produces unexpected results to overcome a *prima facie* case of obviousness, but that in a declaration submitted by Appellant, inventor Sitharaman states that the concentration of Mn in the magnetic composition recited in claim 66 "is a range of concentration that creates an unexpectedly good results for MRI." (Declaration, ¶ 19.) Because Dr. Sitharaman fails to provide more explanation and does not cite to any evidence in support of this assertion, this conclusory statement is unpersuasive.

Appellant fails to persuade us that the Examiner erred. Accordingly, we affirm the rejection of claim 66.

Claim 47

Along with claim 66, the Examiner rejected independent claim 47 and claims 48 and 50–53, which depend on claim 47, under 35 U.S.C. § 103(a) as being unpatentable over Sarmeo, Lee, Wang, and Dai. (*See* Final Act. 3–7.)

Appellant's claim 47 recites:

> A composition for use with magnetic resonance imaging, comprising:
>
> (i) a sufficient amount of the magnetic composition comprising a magnetic metal intercalated in an oxidized graphene nanostructure or a graphitic nano- or microstructure, wherein said magnetic metal comprises Mn, wherein the composition is configured to maintain a water proton relaxivity ratio of r2:r1 <4 and is configured to increase

> the r1 relaxivity by a factor of 2 or more as compared to Mn2+ ion in aqueous media; and
>
> (ii) one or more physiologically acceptable carriers or excipients.

(Appeal App. Br. 10.) Claim 47 is similar to claim 66, but instead of being limited to a range of concentrations of Mn, claim 47 is limited to how the composition is configured to achieve specific results. Specifically, the composition of claim 47 is limited to being "configured to maintain a water proton relaxivity ratio of r2:r1 <4" and being "configured to increase the r1 relaxivity by a factor of 2 or more as compared to Mn2+ ion in aqueous media."

The Examiner finds that Lee teaches Mn-containing graphene MRI compositions have a relaxivity of about 10 $mM^{-1}s^{-1}$. (*See* Ans. 4.) We do not agree. The Examiner cites to the abstract and paragraph 37 of Lee, but Lee does not mention a relaxivity for Mn in either of these locations. The Examiner also cites to Figures 4A and 4B of Lee. (*See id.*) Figures 4A and 4B are reproduced below.

FIG. 4A

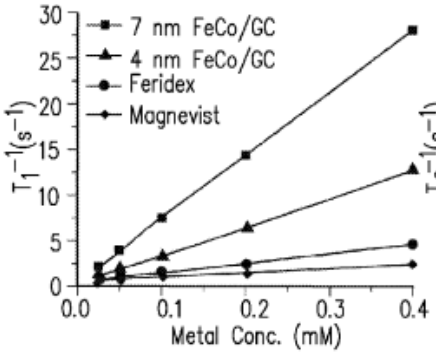

FIG. 4B

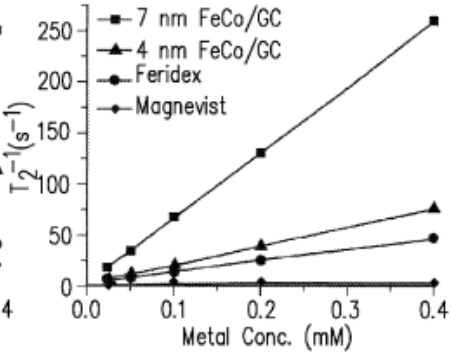

Figure 4A shows T_1-$1^{(s-1)}$ on the y-axis as a function of metal concentration, shown on the X-axis. Similarly, Figure 4B shows T_2-$1^{(s-1)}$ on the y-axis as a

function of metal concentration, shown on the x-axis. Data regarding three CAs (FeCo at two sizes, Feridex (an iron complex (*see* Lee ¶ 105)), and Magnevist (a gadolinium complex (*see id.* at ¶ 104)), are plotted using these axes in Figures 4A and 4B to produce lines having different slopes.

According to Appellant's Specification, relaxivity (r_1), the measure of the efficacy of a CA, is expressed as a function of the concentration of the CA. That is, $r_1=R_1-R_0/[Mn^{+2}]$ and $r_2=R_2-R_0/[Mn^{+2}]$. (*See* Spec. ¶ 86.) Thus, the relaxivities, r_1 and r_2, of the different CAs tested are shown as the different slopes of the lines connecting the points for the measured relaxation rates (T_1^{-1} and T_2^{-1}) at different metal concentrations.

Although r_1 and r_2 might be determined for FeCo/GC, Feridex, and Magnevist from the Figures 4A and 4B, Lee does not provide any data for a Mn complex. The Examiner fails to explain how one could know the slope of a line for a Mn composition without data for the specific compound. The Examiner does not point to any other portion of Lee that reports an r_1 or r_2 for a Mn complex. We agree with Appellant that the Examiner has failed to show that Mn-containing graphene MRI compositions have a relaxivity of about 10 $mM^{-1}s^{-1}$. (*See* Appeal App. Br. 4.) Accordingly, we agree with Appellant that the Examiner has failed to show why one of ordinary skill in the art would have considered it obvious to configure a composition of a Mn intercalated in an oxidized graphene nanostructure or a graphitic nano- or microstructure to maintain a water proton relaxivity ratio of r2:r1<4.

Appellant's Specification states that Mn^{+2} was a known substitute for T1 MRI CAs that include Gd^{+3} (*see* Spec. ¶¶ 5–6) and Dr. Sitharaman states that T1 contrast agents typically have a r2:r1 < 4 (*see* Decl. ¶ 10), but the Examiner fails to provide evidence that one of ordinary skill would expect

this property for a composition of Mn intercalated in an oxidized graphene nanostructure or a graphitic nano- or microstructure.

Because we agree that the Examiner's reasoning was based on the erroneous factual finding that Lee teaches that Mn-based MRI CAs have a relaxivity r1 of about 10 $mM^{-1}s^{-1}$, we reverse the Examiner's rejection of claim 47 and the claims that depend on it.

Double-Patenting

The Examiner also entered two rejections under the doctrine of obviousness-type double-patenting: (1) claims 47, 48, 50–52, and 66 over claims 1–12 of U.S. Patent No. 9,713,650 B2 (Final Act. 8) and (2) claims 47, 48 and 50–52 over claims 1–16 and 23–27 of U.S. Patent No. 9,833,522 B2 (*id.*). Appellant does not address these rejections or raise any argument against them. (*See* Appeal App. Br. 2.) Accordingly, we summarily sustain and, therefore, affirm the rejections. *See* Manual of Patent Examining Procedure § 1205.2 ("If a ground of rejection stated by the examiner is not addressed in the appellant's brief, appellant has waived any challenge to that ground of rejection and the Board may summarily sustain it, unless the examiner subsequently withdrew the rejection in the examiner's answer. *See* 37 CFR 41.39(a)(1).").

Conclusion

We affirm-in-part the rejections of Appellant's claims. In summary:

Claims Rejected	**Basis**	**Affirmed**	**Reversed**
47, 48, 50–53, and 66	35 U.S.C. § 103 over Sarmeo, Lee, Wang, and Dai	66	47, 48, 50–53

Claims Rejected	Basis	Affirmed	Reversed
47, 48, 50–52, and 66	Obvious-type double-patenting over claims 1-12 of U.S. Patent No. 9,713,650 B2	47, 48, 50–52, and 66	
47, 48 and 50–52	Obvious-type double-patenting over 1–16 and 23–27 of U.S. Patent No. 9,833,522 B2	47, 48 and 50–52	
Overall Outcome		47, 48, 50–52, and 66	53

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

AFFIRMED-IN-PART