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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MARTIN GILBERT POMPER,
HYO-EUN BHANG, and PAUL FISHER

Appeal 2018-007074
Application 13/881,777
Technology Center 1600

Before ERIC B. GRIMES, JEFFREY N. FREDMAN, and ULRIKE W. JENKS, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134 involving claims to a method of imaging tumors or cancerous tissue in a subject. The Examiner rejected the claims as non-enabled and as obvious. 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. Appellant identifies the Real Party in Interest as "The Johns Hopkins University and Virginia Commonwealth University" (*see* App. Br. 2).

[2] We have considered and refer to the Specification of Apr. 26, 2013 ("Spec."); Final Action of Nov. 1, 2016 ("Final Act."); Appeal Brief of May 19, 2017 ("App. Br."); Examiner's Answer of Apr. 30, 2018 ("Ans."); and Reply Brief of June 29, 2018 ("Reply Br.").

Statement of the Case

Background

"Targeted imaging of cancer remains an important but elusive goal. Such imaging could provide early diagnosis, detection of metastasis, aid treatment planning and benefit therapeutic monitoring" (Spec. 1:13–15). "Indirect methods use a reporter transgene strategy, in analogy to the use of green fluorescent protein (GFP) in vitro, to provide a read-out on cellular processes occurring in vivo by use of an external imaging device" (*id.* 1:23–25). "Unfortunately, to date, none of these techniques has provided sufficient specific localization of imaging agents, and unacceptably high background noise is still prevalent" (*id.* 1:29–2:2).

The Claims

Claims 1, 3–6, 9–12, 16, 28, and 31–33 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method of imaging tumors or cancerous tissue in a subject, the method comprising the steps of:
>
> (a) administering systemically to the subject a non-viral plasmid nucleic acid construct comprising an imaging reporter gene operably linked to a cancer specific or a cancer selective promoter,
>
> (i) wherein the imaging reporter gene is a herpes simplex virus 1 thymidine kinase (HSV1-tk) or a sodium-iodide symporter (NIS) gene, and
>
> (ii) wherein the cancer specific or the cancer selective promoter is selected from the group consisting of progression elevated gene-3 (PEG-3) promoter and astrocyte elevated gene 1 (AEG-1) promoter;
>
> (b) administering to the subject of part (a) before, after, or together with the construct an imaging agent that is complementary to the imaging reporter gene; and

> (c) screening the subject of part (b) for a signal from the imaging agent, thereby imaging the tumors or the cancerous tissue if present in the subject, wherein if the cancer specific or the cancer selective promoter is AEG-1, the tumors or the cancerous tissue are selected from the group consisting of hepatocarcinoma, breast cancer, lung cancer, prostate cancer, colorectal cancer, glioma, melanoma, and neuroblastoma.

The Issues

A. The Examiner rejected claims 1, 3–6, 9–12, 16, 28, and 31–33 under 35 U.S.C. § 112, first paragraph, enablement (Ans. 5–15).

B. The Examiner rejected claims 1, 3, 6, 11, 12, 16, and 28 under 35 U.S.C. § 103(a) as obvious over Brody,[3] Fisher,[4] Sarker,[5] and Su[6] (Ans. 15–16).

C. The Examiner rejected claims 5, 9, 10, 32, and 33 under 35 U.S.C. § 103(a) as obvious over Brody, Fisher, Sarker, Su, Pasqualini,[7] and Nimmagadda[8] (Ans. 17–18).

D. The Examiner rejected claim 31 under 35 U.S.C. § 103(a) as obvious over Brody, Fisher, Sarker, Su, and Chen[9] (Ans. 19–20).

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[3] Brody et al., US 2012/0149647 A1, published June 14, 2012.
[4] Fisher et al., US 2011/0313028 A1, published Dec. 22, 2011.
[5] Sarkar et al., *Eradication of Therapy-Resistant Human Prostate Tumors Using a Cancer Terminator Virus*, 67 Cancer Res. 5434–42 (2007).
[6] Su et al., *Targeting gene expression selectively in cancer cells by using the progression-elevated gene-3 promoter*, 102 PNAS 1059–64 (2005).
[7] Pasqualini et al., US 2010/0254896 A1, published Oct. 7, 2010.
[8] Nimmagadda et al., *Herpes Simplex Virus Thymidine Kinase Imaging in Mice with (1-(2'-deoxy-2'-[^{18}F] fluoro-1-β-D-arabinofuranosyl)-5-iodouracil) and metabolite (1-(2'-deoxy-2'-[^{18}F] fluoro-1-β-D-arabinofuranosyl)-5-uracil)*, 36 Eur. J. Nucl. Med. Mol. Imaging 1987–93 (2009).

E. The Examiner rejected claims 1, 3–6, 9–12, 16, 28, and 31–33 on the ground of provisional obviousness-type double patenting over claims 1–10 and 14 of US application 14/182,690 (Ans. 18).

A. 35 U.S.C. § 112, first paragraph, enablement

The Examiner finds "because the art of delivering DNA, molecular imaging i.e. detection of signal and the correlation of small animal models and humans in this art is proven and known to be unpredictable in the art, the invention is not enabled" (Ans. 8).

Appellant contends the

> Examiner's reliance on various references in support of the rejection is wholly misplaced. In some cases, the references relate to methods of gene therapy, and not cancer imaging, and are not relevant to the pending claims. In some cases, the references are outdated and do not represent the current state of the art. In all cases, the Examiner cites teachings of the references out of context and exaggerates technical considerations raised by the authors to the level of impassable obstacle.

(App. Br. 5–6).

The issue with respect to this rejection is: Does a preponderance of the evidence of record support the Examiner's conclusion that the Specification does not enable the claimed invention?

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[9] Chen et al., *The sodium/iodide symporter and radio-iodide therapy*, 25 Foreign Medical Sciences. Section of Radiation Medicine and Nuclear Medicine 258–61 (2001) (abstract only).

Findings of Fact

Breadth of Claims

1. Claim 1, the sole independent claim, is drawn to systemic administration of a non-viral plasmid nucleic acid construct with one of two specific imaging reporter genes, HSV1-tk or NIS, linked to one of two specific cancer promoters, PEG-3 or AEG-1, in order to image cancers or tumors.

Presence of Working Examples

2. Example 1 of the Specification teaches systemic DNA delivery of a plasmid with a PEG-3 promoter and HSV1tk reporter gene by injection "into the lateral tail vein of an animal" (Spec. 30:15–29). Example 1 teaches that imaging studies and immunohistochemistry was performed on animals with induced tumors (Spec. 32:7–27). Example 1 teaches "[e]xpression of Luc driven by PEG-Prom was observed only in the melanoma metastasis model (Mel) and not in control animals" (Spec. 33:18–19).

3. Example 1 of the Specification teaches

> to exclude the possibility that tumor-specific expression of Luc . . . might have resulted from the difference in transfection efficiency between normal and malignant mouse lung tissues, we quantified the amount of pDNA delivered to the lung of each animal . . . That result confirmed that the tumor-specific expression of Luc observed in these models was due to the tumor-selective activity of PEG-Prom rather than differential transfection efficiency between normal and malignant lungs. Poor vascularization and segregated large nodules most likely contributed to lower transfection efficiency observed in the lung of the BCa model.

(Spec. 34:18–29).

4. Example 1 of the Specification teaches bioluminescence imaging (BLI) "with systemically administered pPEG-Luc also enabled imaging of small metastatic deposits, i.e., micrometastases, outside of the lung parenchyma in both the Mel and BCa models. That was confirmed through harvesting regions producing BLI signal above background and performing correlative histological analysis" (Spec. 35:8–11).

5. Example 1 of the Specification teaches

> we generated a more clinically relevant PEG-Prom-driven gene expression imaging system, pPEG-HSV1 tk . . . which can be detected using radionuclide-based techniques, namely, single photon emission computed tomography (SPECT) or positron emission tomography (PET), upon administration of a suitably radiolabeled nucleoside analog. . . . We further confirmed tumor presence in presumptive extrathoracic metastatic sites through gross histological analysis after the 48 h imaging session. Detected on the whole body SPECT-CT images . . . were multiple metastatic lesions in the dorsal neck of Mel-2 that corresponded to the intact histological specimen.

(Spec. 35:24–36:10).

Amount of Direction or Guidance Presented

6. The Specification provides diagrams of specific imaging constructs including one of the cancer promoters and both of the imaging genes recited in claim 1 (*see* Figures 1A and 1B).

7. The Specification teaches that for "systemic distribution of the vector, the preferred routes of administration include but are not limited to: intravenous, by injection, transdermal, via inhalation or intranasally, or via injection or intravenous administration of a cationic polymer-based vehicle (e.g. vivo-jetPEI™). Liposomal delivery, which when combined with targeting moieties will permit enhanced delivery" (Spec. 24:6–10).

8. The Specification teaches "optimal or effective tumor-inhibiting or tumor-killing amounts are established e.g. during animal trials and during standard clinical trials. Those of skill in the art are familiar with conversion of doses e.g. from a mouse to a human" (Spec. 24:27–29). The Specification provides conversion factors for relative doses (*see* Spec. 25:5–15).

Relative skill in the art

9. The Examiner finds the "level of skill is high for this invention. It requires administration of DNA and agents to a subject in order to detect cancer cells throughout the body" (Ans. 7).

State of the Prior Art and Unpredictability of the Art

10. Frangioni[10] teaches the "goal of this review is to inform the reader about why current imaging modalities are generally inadequate for oncology and which new technologies have the potential to improve patient care" (Frangioni 4013, col. 1).

11. Frangioni teaches imaging technologies including ultrasound, X-Ray imaging, MRI, SPECT, PET, and optical imaging (*see* Frangioni 4014–5), but does not discuss the use of nucleic acid constructs with reporter genes. Frangioni teaches:

> the body has many barriers to the effective targeting of contrast agents (and therapeutics) in vivo, including inhibitors present in plasma, a relatively small effective endothelial pore size (hydrodynamic diameter of approximately 5 nm) that constrains biodistribution, and basement membranes that act as barriers to preinvasive cancer detection. Finally, many solid tumors have high hydrostatic pressure, which impedes homogeneous infiltration of diagnostic agents.

[10] Frangioni, *New Technologies for Human Cancer Imaging*, 26 J. Clin. Oncology 4012–4021 (2008).

(Frangioni 4014, col. 1).

12. Frangioni teaches the "detection and imaging of small numbers of cancer cells anywhere in the human body remains elusive. Although new technologies, such as optical imaging, will likely play an important role in certain clinical applications, the field of oncology needs a revolutionary advance in the physics and chemistry of tumor detection" (Frangioni 4019, col. 2).

13. Close[11] teaches the "challenge of detecting and locating bioluminescent light emissions from within living subjects has been met by several commercial suppliers of *in vivo* imaging equipment . . . When superimposed, regions of bioluminescence become mapped to the subject's anatomy for pinpoint identification of source emissions" (Close 183).

14. Min[12] teaches "[n]aked therapeutic genetic molecules are generally difficult to deliver primarily due to rapid clearance" but explains that "specialized gene delivery vehicles (GDV) that improve delivery efficiency and cell-specificity are preferred" (Min 15, col. 2).

15. Min teaches the "HSV1-tk gene has been utilized as an effective reporter gene for nuclear imaging using PET or a gamma camera" (Min 20, col. 1).

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[11] Close et al., *In Vivo Bioluminescent Imaging (BLI): Noninvasive Visualization and Interrogation of Biological Processes in Living Animals*, 11 Sensors 180–206 (2011).
[12] Min et al., *Molecular Imaging of Biological Gene Delivery Vehicles for Targeted Cancer Therapy: Beyond Viral Vectors*, 44 Nuclear Med. Molecular Imaging 15–24 (2010).

16. McCrudden[13] teaches "systemic therapeutics bypass the skin, but encounter further extracellular barriers before reaching their site of action . . . Whilst in the circulation, however, non-viral agents can be subject to non-specific binding by serum proteins, which can result in aggregation or dissociation of nanoparticles" (McCrudden 216).

17. McCrudden teaches:

> It is apparent that the field of non-viral gene delivery is making significant progress in the quest for the ideal gene delivery vehicle. What is also evident is that the most successful systems are designed to overcome many biological barriers and as a consequence the traditional single function systems are now rendered obsolete. Viruses are nature's perfect delivery vehicle and provide the inspiration to many non-viral gene therapy researchers in the design of state of the art multi-faceted vehicles. Through a greater understanding and appreciation of the biological barriers to systemic gene delivery, non- viral gene therapy researchers are on the cusp of creating a variety of highly efficient vehicles that will revolutionise cancer gene therapy.

(McCrudden 234).

18. Thomas[14] teaches "[v]ector TROPISM, the duration of transgene expression and vector immunogenicity are other factors that influence the suitability of a vector for specific therapeutic applications" (Thomas 348, col. 2).

19. Thomas teaches "[a]t the present time, viral vectors are the best available vehicles for efficient gene transfer into most tissues. Nonviral

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[13] McCrudden et al., *Cancer Gene Therapy – Key Biological Concepts in the Design of Multifunctional Non-Viral Delivery Systems*, http://dx.doi.org/10.5772/54271 213–48 (2013).
[14] Thomas et al., *Progress And Problems With The Use Of Viral Vectors For Gene Therapy*, 4 Nature Genetics 346–58 (2003).

gene delivery is potentially safer than viral-mediated delivery, but — with the exception of a few promising applications, such as vaccines — non-viral systems are, at present, limited by their inefficiency" (Thomas 356, col. 2).

20. Croft[15] teaches "[i]maging of animal tumors may be accomplished by all of the ordinary techniques for imaging human tumors . . . Optical techniques have become popular because they require less expensive equipment and less animal preparation than do the more instrument-intensive MRI and PET" (Croft 367, col. 2).

21. Croft teaches "HSV-thymidine kinase (TK) often is used for such purposes, targeting TK receptors, which makes possible the use of anti-HSV drugs as imaging and targeting agents" (Croft 373, col. 1).

22. Lee[16] teaches:

> Common transfection techniques were developed for in-vitro, microscopic volume sample. It can be impractically expensive to applied to small animal work as well as inefficient, because the small animal has relatively large body volume but very little surface area to be exposed to agents (chemical or viral) for transfection. A second obstacle is that the expression in this case can often be transient, due to the inability of the living tissue to regulate the excessive protein and to replicate the DNA. With the reporter gene not stably incorporated into the animal genome, the signal can have relatively very short (less than 2 days) life span.

(Lee 2, col. 1).

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[15] Croft, *Animal models for imaging*, 18 Disease Markers 365–74 (2002).
[16] Lee, *The Advantages of Fluorescent Proteins over Luciferase for In Vivo Imaging*, Focal Points Application Note FP-129 14 (2008).

Quantity of Experimentation

23. The Examiner finds that the "quantity of experimentation needed to make or use the invention based on the content of the disclosure is quite high as there are numerous art provided for obstacles to performing the metho[do]logy" (Ans. 8).

24. The Specification teaches "[b]ased on these experiments it can be seen that the systemic delivery of PEG-Prom-driven imaging constructs will enable tumor-specific expression of reporter genes, not only within primary tumor, but also in associated metastases in a manner broadly applicable to tumors of different tissue origin or subtype" (Spec. 30:10–14).

Principles of Law

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.

In re Wright, 999 F.2d 1557, 1561–62 (Fed. Cir. 1993).

> Factors to be considered in determining whether a disclosure would require undue experimentation … include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

Analysis

In addressing the *Wands* factors, we find that the balance of factors does not support the Examiner's position. The claims are narrow in scope, limited to systemic administration with particular imaging reporter genes

and promoters and limited to particular cancers (FF 1). There are working examples (FF 2–5) as well as detailed guidance in the Specification (FF 6–8) in a highly skilled art (FF 9). There is only the Examiner's statement that a large quantity of experimentation would be required (FF 23) while the Specification suggests that the experiments disclosed are sufficient (FF 24).

There is limited evidence of specific unpredictability related to systemic imaging using the claimed nucleic acid constructs. Frangioni teaches general imaging difficulties (FF 10–12), while Min teaches issues in delivery of nucleic acid constructs (FF 14). McCrudden and Thomas teach that there have been issues with administration of DNA that requires entry into cells and expression in cells for activity including dissociation of the particles being administered and non-specific targeting (FF 16–19).

However, Min also teaches HSV1-tk has been used as an effective reporter gene (FF 15) as does Croft (FF 21). And while Lee teaches administration may be expensive and transient, there is no showing that the expense is undue in a medical context. Also, imaging for diagnostic purposes is desirably transient since there is no need for long term expression of the reporter genes in patients after the diagnosis is complete (FF 22). Moreover, the art cited in the obviousness rejection, including Brody, provides a detailed discussion supporting enablement of the claims (*see* FF 25–30 below).

Therefore, in light of the detailed working examples and disclosure in the Specification, the limited and predictable amount of experimentation necessary, and the narrow breadth of claim 1, we agree with the Appellant that the evidence supports the position that the Specification enables the scope of the claims. *See In re Fisher*, 427 F.2d 833, 839 (CCPA 1970)

("[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.").

B. 35 U.S.C. § 103(a) over Brody, Fisher, Sarker, and Su

The Examiner finds Brody teaches "methods of imaging tumors in mice wherein non-viral vectors and luciferase are administered intravenously (which is a form of systemic administration) . . . The luciferase was delivered with PEI . . . Delivery can be to any tumor types such as ovarian or breast" (Ans. 15–16).

The Examiner acknowledges that Brody doesn't teach the "use of PEG-3 or AEG-1 as promoters" (Ans. 16). The Examiner finds that Fisher "teaches delivery of non-viral plasmid vectors with use of PEG-3 and CCN1/2 linked to reporter/imaging gene for *in vivo* imaging. The promoter can be PEG-3 or AEG-1" (*id.*). The Examiner finds Su teaches "targeted gene expression using a PEG3-luciferase vector" (*id.*). The Examiner finds Sarker teaches the "use of an AEG-1 luciferase vector" (*id.*).

The Examiner finds it obvious to combine Brody

> with the promoters of Sarker, Su and Fisher as Brody is directed to method of targeting tumor cells wherein expression is limited to these cells and wherein Sarker, Su and Fisher teaches that it is within the ordinary skill of the art to deliver vectors comprising cancer specific promoters for imaging. One would have been motivated to do so in order to receive the expected benefit of using proven and reliable imaging techniques.

(Ans. 16).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Brody, Fisher, Su, and Sarkar renders the claims obvious?

Findings of Fact

25. Brody teaches a "bioluminescence imaging system (MS™ Imaging System, Xenogen Corp.) can be used to image mice and detect nanoparticle-delivered Luc gene expression" (Brody ¶ 213).

26. Brody teaches an imaging process in which "C32-MSLN/firefly luciferase DNA (Fluc) nanoparticles were directly injected into subcutaneous xenografts derived from MSLN+ ovarian tumor cells, C32, to poly(β-amino ester) polymer, or PEI was complexed to MSLN/Fluc DNA to generate nanoparticles. Mice were optically imaged and bioluminescence was detected in tumors 6 hrs after injection" (Brody ¶ 202).

27. Brody teaches vectors that may contain "the herpes simplex virus thymidine kinase gene, HSV-tk, and/or a marker gene" (Brody ¶ 61).

28. Brody teaches vectors may express genes using "a cancer specific promoter" (Brody ¶ 51).

29. Brody teaches "constructs containing the luciferase (Luc) sequence in place of DT-A allows the use of optical imaging to evaluate gene expression in multiple organs easily" (Brody ¶ 219).

30. Brody teaches the "pharmaceutical composition may be administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated . . . [including] parenterally, for example by intravenous drip" (Brody ¶ 106).

31. Brody teaches the "disclosed compositions can be used to treat cancers including, but not limited to, pancreatic cancer, ovarian cancer, breast cancer, non-small cell lung cancer, and liver cancer" (Brody ¶ 10).

32. Brody teaches:

> There are a number of compositions and methods which can be used to deliver nucleic acids to cells, either in vitro or in vivo. These methods and compositions can largely be broken down into two classes: viral based delivery systems and non-viral based delivery systems. For example, the nucleic acids can be delivered through a number of direct delivery systems such as, electroporation, lipofection, calcium phosphate precipitation, plasmids, viral vectors, viral nucleic acids, phage nucleic acids, phages, cosmids, or via transfer of genetic material in cells or carriers such as cationic liposomes.

(Brody ¶ 48).

33. Fisher teaches the "use of the cancer specific promoter such as the CCN1/2, PEG-3, or AEG-1 promoter, will allow selective expression of the gene product in the cancer cell" (Fisher ¶ 100).

34. Su teaches "the use of the PEG-Prom as a means of selectively targeting gene expression in human tumor cells for directed cancer gene therapy applications" (Su 1060, col. 1).

35. Su teaches forming a vector comprising PEG-3 promoter linked to the luciferase gene (see Su 1060, col. 1).

Principles 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).

Analysis

We adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Ans. 15–16; FF 25–35) and agree that the claims are rendered obvious by Brody, Fisher, Su, and Sarkar. We address Appellant's arguments below.

Appellant contends "the combined references do not teach or suggest methods of imaging tumors or cancerous tissue in a subject comprising systemic administration of a nonviral plasmid nucleic acid construct" (App. Br. 17).

We find this argument unpersuasive because Brody teaches "constructs containing the luciferase (Luc) sequence in place of DT-A allows the use of optical imaging to evaluate gene expression in multiple organs easily" (FF 29) and expressly suggests the constructs "may be administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated . . . [including] parenterally, for example by intravenous drip" (FF 30). Brody's teaching to optically image multiple organs using a luciferase construct along with the general suggestion to administer compositions systemically reasonably suggests systemic administration of the luciferase construct for imaging multiple organs (FF 25, 29, 30). Brody also teaches both "viral based delivery systems and non-viral based delivery systems" (FF 32).

Appellant contends that Brody only teaches "'nanoparticles were **directly injected into subcutaneous xenografts** derived from MSLN+ ovarian tumor cells.' Brody, paragraph [0201] (emphasis added). Hence, the reference teaches only *direct administration* of compositions for imaging" (App. Br. 17).

While Appellant is correct that Brody only exemplifies imaging using direct injection of constructs (FF 26), Brody expressly suggests that constructs may be administered to multiple organs (FF 29) and also suggests systemic administration of constructs (FF 30). "A disclosure in a reference is not limited to its specific illustrative examples, but must be considered as a whole to ascertain what would be realistically suggested thereby to one of ordinary skill in the art." *In re Uhlig*, 376 F.2d 320, 323 (CCPA 1967). Indeed, "[a]ll the disclosures in a reference must be evaluated, including nonpreferred embodiments . . . and a reference is not limited to the disclosure of specific working examples." *In re Mills*, 470 F.2d 649, 651 (CCPA 1972). Thus, the issue is not whether Brody provides an example of systemic administration but rather whether Brody suggests systemic administration of the nucleic acids. Brody does so (FF 30).

Appellant contends that "[p]aragraph [0010] describes the delivery of therapeutic agents, *not luciferase*, to treat, *not image*, various cancers" (App. Br. 18). Appellant contends "[p]aragraph [0048] describes the direct delivery of plasmid vectors to target cells, and *not* systemic administration. Paragraph [0107] describes fluid vehicles suitable for in intravenous administration generally" (*id.*).

We are not persuaded by this argument as "picking and choosing may be entirely proper in the making of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence" *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). That is, Brody teaches an example where nucleic acid constructs were administered into animals in order to image tumors (FF 26), Brody suggests that nucleic acid constructs may be used to evaluate and image multiple organs (FF 29), and Brody

suggests that nucleic acid constructs may be administered systemically (FF 30). We agree with the Examiner that the ordinary artisan, familiar with these teachings in Brody, would have reasonably found it obvious to administer Brody's nucleic acids systemically in order to image tumors in multiple organs consistent with the disclosures of Brody (FF 25–31). Appellant's Appeal Brief does not identify any objective evidence that would rebut the Examiner's obviousness position.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that Brody, Fisher, Su, and Sarkar renders the claims obvious.

C. and D. 35 U.S.C. § 103(a) over Brody, Fisher, Sarker, Su, Pasqualini, and Nimmagadda and/or Chen

Appellant relies upon the same reasoning regarding the absence of a teaching of systemic administration as discussed above with regard to Brody, Fisher, Sarker, and Su for these further rejections. Appellant contends "the combined references do not teach or suggest methods of imaging tumors or cancerous tissue in a subject comprising systemic administration of a nonviral plasmid nucleic acid construct" (App. Br. 19; *cf.* Reply Br. 4, 9). We remain unpersuaded by these arguments for the reasons given above.

E. Provisional Obviousness-Type Double Patenting

We summarily affirm the provisional obviousness-type double patenting rejections because Appellant does not dispute the merits of this rejection. *See* Manual of Patent Examining Procedure § 1205.02 ("If a

ground of rejection stated by the examiner is not addressed in the appellant's brief, that ground of rejection will be summarily sustained by the Board.")

CONCLUSION

In summary:

Claim(s) Rejected	Basis	Affirmed	Reversed
1, 3–6, 9–12, 16, 28, 31–33	§ 112, ¶ 1, enablement		1, 3–6, 9–12, 16, 28, 31–33
1, 3, 6, 11, 12, 16, 28	§ 103(a) Brody, Fisher, Sarker, Su	1, 3, 6, 11, 12, 16, 28	
5, 9, 10, 32, 33	§ 103(a) Brody, Fisher, Sarker, Su, Pasqualini, Nimmagadda	5, 9, 10, 32, 33	
31	§ 103(a) Brody, Fisher, Sarker, Su, Pasqualini, Nimmagadda, Chen	31	
1, 3–6, 9–12, 16, 28, 31–33	Provisional Obviousness-type Double Patenting	1, 3–6, 9–12, 16, 28, 31–33	
Overall Outcome		1, 3–6, 9–12, 16, 28, 31–33	

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