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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte M.G. FINN, STEVEN BROWN, and JASON FIEDLER

Appeal 2017-001118[1]
Application 13/882,773
Technology Center 1600

Before JEFFREY N. FREDMAN, TAWEN CHANG, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an Appeal under 35 U.S.C. § 134 involving claims to a synthetic capsule construct for providing a protected chemical milieu. The Examiner rejected the claims as anticipated and as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse and enter a new ground of rejection.

Statement of the Case

Background

"Artificial encapsulation or immobilization on solid supports has been shown to confer stability as well as facilitate purification and reuse" (Spec. 1:20–21). "One aspect of the present invention is directed to protein nano-

[1] Appellants identify Qapsule Technologies, Inc. as the real party in interest (*see* App. Br. 3).

particles that encapsulate cargo proteins within an enclosure containing a protected chemical milieu. Encapsulation within such protected chemical milieu can impart enhanced employability and performance to cargo proteins, particularly within otherwise harsh chemical environments" (Spec. 3:3–7).

The Claims

Claims 1–8, 11–18, 31–36, and 38 are on Appeal.[2] Independent claim 1 is representative and read as follows:

> 1. A synthetic capsule construct for providing a protected chemical milieu, the construct comprising:
>
> a shell having a plurality of shell proteins, said plurality of shell proteins being assembled with one another for forming said shell and defining an enclosure therein, each of said shell proteins, when assembled for forming said shell, having an interior surface facing inwardly toward said enclosure and an exterior surface facing outwardly away from said enclosure, said shell serving to restrict permeability to and from said enclosure for providing the protected chemical milieu therein, said shell proteins being recombinant;
>
> a cargo protein, said cargo protein being recombinant and optionally including a peptide tag; and
>
> a bifunctional polynucleotide having both a first aptameric activity for binding said cargo protein and a second aptameric activity for retaining said bifunctional polynucleotide within said enclosure by assembly with the interior surface of said shell protein,
>
> said bifunctional polynucleotide being non-naturally occurring; said bifunctional polynucleotide serving to link said cargo protein within said enclosure for providing the said cargo protein with the protected chemical milieu therein.

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[2] Claim 37 is objected to, but is not subject to a rejection (*see* Final Act. 8).

The Issues

A. The Examiner rejected claims 1–5, 7, 8, 11–18, 31–33, 35, and 38 under 35 U.S.C. § 102(b) as anticipated by Young[3] (Final Act. 3–6).

B. The Examiner rejected claims 1–3, 5, 7, 8, 13–18, and 31–36 under 35 U.S.C. § 103(a) as obvious over Young and Brown[4] (Final Act. 6–7).

C. The Examiner rejected claims 1, 5, and 6 under 35 U.S.C. § 103(a) as obvious over Young, Brown, Lim,[5] and Spingola[6] (Final Act. 7–8).

Because the same issue is dispositive for all of these rejections, we will consider them together. The Examiner finds Young teaches

> protein cages as delivery vehicles for selective entrapment and release of materials [0021], wherein the proteinaceous shell sell-assembles to form a protein cage which protein cage may be obtained from a non-viral or viral source [0026]. The protein cage may be linked to the therapeutic cargo agent via a bifunctional nucleic acid linker [0112].

(Final Act. 3).

Appellants contend

> 1. Young does not disclose or suggest that the porosity of his protein cages is sufficient for loading a **cargo protein** therein; Young discloses loading only small molecule imaging agents and therapeutics into his protein cages,

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[3] Young et al., US 2009/0041671 A1, published Feb. 12, 2009.
[4] Brown et al., *RNA Bacteriophage Capsid-Mediated Drug Delivery and Epitope Presentation*, 45 INTERVIROLOGY 371–80 (2002)
[5] Lim et al., *The RNA-binding Site of Bacteriophage Qβ Coat Protein*, 271 J. BIOLOGICAL CHEMISTRY 31839–45 (1996).
[6] Spingola et al., *MS2 coat protein mutants which bind Qβ RNA*, 25 NUCLEIC ACIDS RESEARCH 2808–15 (1997).

2. Young does not disclose or suggest a **recombinant cargo protein** and does not disclose or suggest that, if the cargo were a recombinant protein, then the cargo and capsule proteins would be biosynthesized simultaneously in the same organism and self-assembled therein. Nor does Young disclose or suggest that intracellular self-assembly might be advantageous.
3. Young does not disclose a **recombinant cargo protein having a peptide tag**.
4. Young does not disclose a **bifunctional polynucleotide**.
5. Young does not disclose a **bifunctional polynucleotide having a first aptameric activity for binding the cargo protein**.
6. Young does not disclose a **bifunctional polynucleotide having a second aptameric activity for retaining the bifunctional polynucleotide within the enclosure by assembly with the interior surface of the shell protein.**

(App. Br. 14–15).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Young or Brown teach a polynucleotide having "a first aptameric activity for binding said cargo protein and a second aptameric activity for retaining said bifunctional polynucleotide" as required by claim 1?

Findings of Fact

1. Young teaches "protein cages can be used as constrained reaction vessels for the selective entrapment and release of materials" (Young ¶ 21).

2. Young teaches:

> By "delivery agent" herein is meant a proteinaceous shell that self-assembles to form a protein cage (e.g. a structure with an interior cavity which is either naturally accessible to a solvent or can be made to be so by altering solvent concentration, pH,

> equilibria ratios, etc.), and contains imaging and therapeutic agents

(Young ¶ 26)

3. Figures 1A and 1B of Young are reproduced below:

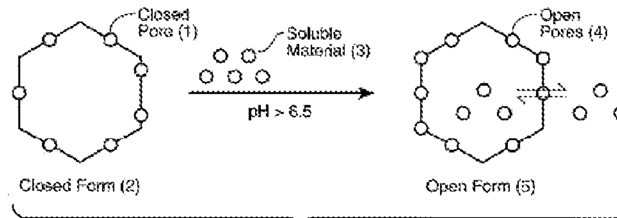

FIG._1A

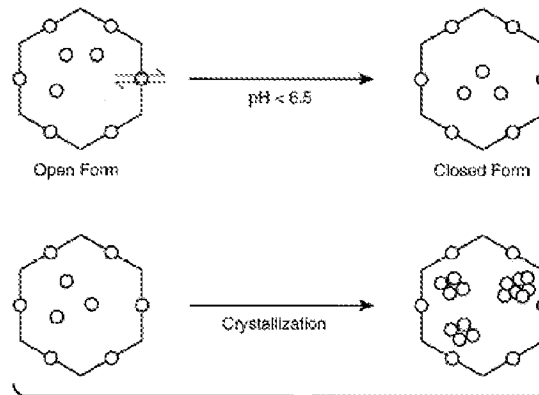

FIG._1B

Figure 1 of Young "illustrates the basic principle of introducing soluble material such as a medical imaging agent into a protein cage." (Young ¶ 15.) Young teaches that

> pH can be used to control the expansion and contraction of the protein cage . . . When the cage is expanded, i.e., opened, pores are formed allowing for the free exchange of soluble material between the inside and outside of the cage (*see* FIG. 1A). When the cage is contracted, i.e., closed, the pores are closed and any material in the cage is trapped within (*see* FIG. 1B).

(Young ¶ 21).

4. Young teaches "a corresponding therapeutically active agent is chosen. These agents will be any of a wide variety of drugs" (Young ¶ 96).

5. Young teaches "therapeutic agents of the present invention may be attached to the protein cage via a linker" (Young ¶ 112).

6. Young teaches:

> In a preferred embodiment, the linker used to attach the imaging agent and therapeutic agents to a protein cage is a polymer . . . The character of the polymer will vary, but what is important is that the polymer either contain or can be modified to contain functional groups for the attachment of the nanoparticles of the invention. Suitable polymers include . . . nucleic acids and their analogs including those with modified ribose-phosphate backbones.

(Young ¶¶ 113–114).

7. The Specification states: "For purposes of the present disclosure, the term 'aptamer' is defined herein to mean an oligonucleotide having binding affinity and/or specificity for a protein tag or a protein binding site" (Spec. 39:23–25).

8. Brown teaches: "To use our knowledge of the three-dimensional structure and self-assembly mechanism of RNA bacteriophage capsids to develop novel virus-like particles (VLPs) for drug delivery and epitope presentation" (Brown 371, Abstract).

9. Brown teaches: "Covalent conjugation has also been used to generate RNA stem-loops attached to the toxin, ricin A chain, or to nucleotide-based drugs, that are still capable of stimulating self-assembly of the capsid in vitro" (Brown 371, Abstract).

Principles of Law

A prior art reference can only anticipate a claim if it discloses all the claimed limitations "arranged or combined in the same way as in the claim." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012).

Analysis

We begin with claim interpretation because before a claim is properly interpreted, its scope cannot be compared to the prior art. In this case, the dispute centers over the term "aptamer" in claim 1.

Appellants contend "[c]ovalent conjugation is not the same as aptameric binding activity" (App. Br. 18) and neither Young nor Brown discloses polynucleotides with aptameric binding activity (*see* App. Br. 15, 18).

The Examiner responds "Young et al. teach that the linker is a nucleic acid polymer, that the nucleic acid polymer is bifunctional binds to or attaches to the cargo protein (therapeutic agent) and to the protein cage (shell protein)" (Ans. 12).

We find that Appellants have the better position. While every "aptamer" is a polynucleotide, consistent with Appellants' definition (FF 7), not every polynucleotide is an "aptamer" with the capability of binding a protein and the capability of binding shell proteins involved in capsid formation. We also agree with Appellants that the ordinary artisan, familiar with the term "aptamer", would recognize that aptameric binding is reasonably understood as noncovalent, hydrogen bonding that is based on the unique primary, secondary, and/or tertiary structures formed by the polynucleotide.

Young teaches covalent attachment of the polymers, specifically that a "polymer either contain or can be modified to contain functional groups for the attachment of the nanoparticles of the invention" (FF 6). There is no indication in Young that the attachment would be by noncovalent aptameric binding. Similarly, Brown teaches covalent attachment to nucleic acids (FF 9). Therefore, neither reference suggests aptameric binding, and the evidence does not support an inherency position that such binding necessarily occurs. "Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *MEHL/Biophile Int'l. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999).

The Examiner provides no specific teaching to use aptameric binding, or any specific reference that inherently and reasonably relies upon aptameric binding to the cargo protein and to the shell protein.

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that Young or Brown teach a polynucleotide having the aptameric activities as required by claim 1.

New Ground of Rejection

Under the provisions of 37 C.F.R. § 41.50(b), we enter the following new ground of rejection.[7] Claims 1, 2, 5, 7, 13–15, 31, 33–35, and 38 are rejected under 35 U.S.C. § 102(b) as anticipated by Perez[8] as evidenced by Mair,[9] Ye,[10] and Gonzalez.[11]

Findings of Fact

10. Perez teaches: "PB1 and PA interact to assemble influenza virus transcription and replication complexes, which also include PB2. . . . [W]e engineered a set of nested deletion mutants within the PB1 N-terminal 48 amino acids" (Perez 8129, col. 2).

11. Table 1 of Perez shows recombinant viruses with PB1 mutations, and is reproduced below:

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[7] As the Board's function is primarily one of review and not search, we leave to the Examiner the determination of whether there is additional prior art to address the remaining dependent claims.

[8] Perez et al., *Functional Analysis of PA Binding by Influenza A Virus PB1: Effects on Polymerase Activity and Viral Infectivity*, 75 J. VIROLOGY 8127–36 (2001).

[9] Mair et al., *Receptor binding and pH stability — How influenza A virus hemagglutinin affects host-specific virus infection*, 1838 BIOCHIMICA ET BIOPHYSICA ACTA 1153–68 (2014).

[10] Ye et al., *Association of Influenza Virus Matrix Protein with Ribonucleoproteins*, 73 J. VIROLOGY 7467–73 (1999).

[11] Gonzalez et al., *Characterization of Influenza Virus PB1 Protein Binding to Viral RNA: Two Separate Regions of the Protein Contribute to the Interaction Domain*, 73 J. VIROLOGY 631–7 (1999).

TABLE 1. Functional assessment of PA-binding mutants of PB1[a]

Strain or mutant	% PA binding (two-hybrid)[b]	P5 polymerase activity (CAT) (%)[b]	PB1 mutant virus yield (PFU/ml)	Plaque purified and sequenced
WT	100	100	4.0×10^7	+
D2V	53 ± 7	0	0	–
V3D	21 ± 8	0	0	–
N4D	22 ± 5	24 ± 1	4.0×10^4	+
P5L[c]		ND[d]	1.0×10^3	+
T6D	75 ± 5	56 ± 4	5.1×10^6	+
L7D[c]	0	21 ± 2	2.0×10^{3e}	+[e]
L8D	0	0		–
F9D	0	3 ± 1	0	–
L10D[c]	0	15 ± 5	2.0×10^{3e}	+[e]
K11D	35 ± 7	48 ± 2	3.0×10^3	+
V12D	40 ± 5	54 ± 7	4.5×10^3	+
P13D	100 ± 2	78 ± 2	1.9×10^5	+
A14D	100 ± 2	0	0	–

"[W]e were able to rescue mutant viruses that displayed detectable and significant polymerase activity. The exception is mutant F9D, which had only a 3% polymerase activity of the WT (Table 1) and thus might be too low for virus rescue" (Perez 8132, col. 1 and 2).

12. Mair, a postfiling date reference,[12] is solely cited to evidence the inherent structure of the influenza virus, with figure 1, panel A, reproduced below:

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[12] MPEP § 2131.01(III) "Extra Reference or Evidence Can Be Used To Show an Inherent Characteristic of the Thing Taught by the Primary Reference."

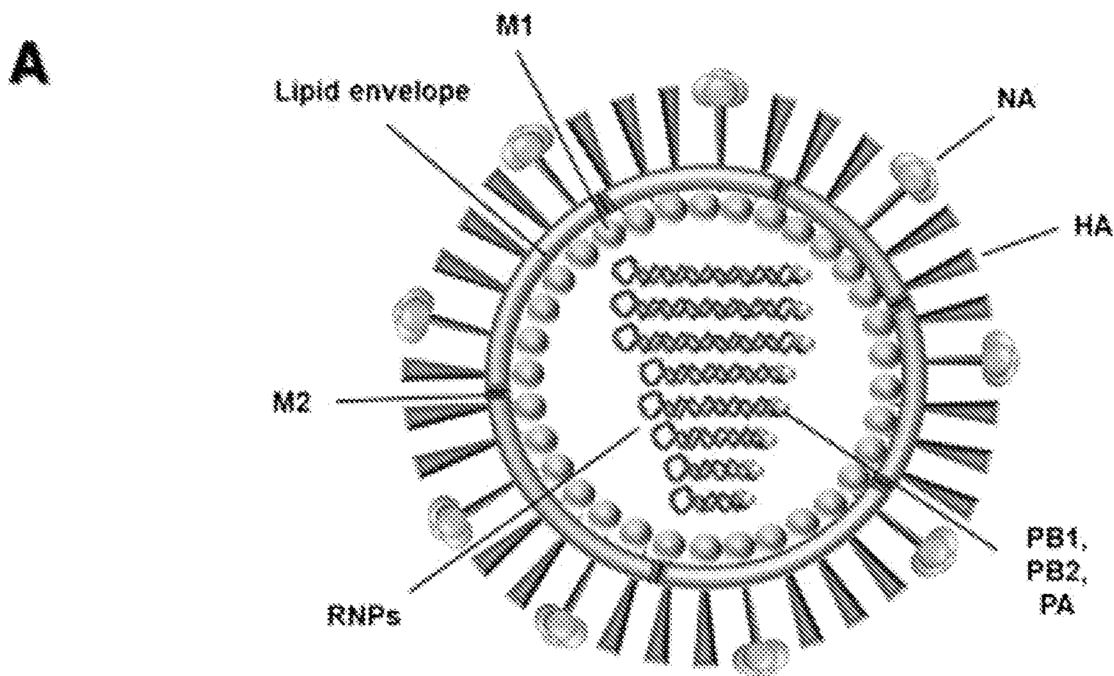

Fig. 1. (A) Schematic representation of an influenza A virus particle. The spike proteins hemagglutinin (HA, blue), neuraminidase (NA, green) and the proton channel protein M2 (violet) are embedded in the lipid envelope (turquoise) of the virus. The membrane is lined with the M1 capsid protein at the inside (yellow). The viral genome consists of eight ribonucleoprotein particles (RNPs, red), with each segment formed by viral RNA (vRNA), the nucleoprotein (NP) and the viral polymerase proteins (PB1, PB2 and PA, colored in gray).

(Mair 1155).

13. Ye is cited to evidence that the influenza virus M1 capsid (or shell) protein binds to the viral RNA, specifically teaching: "Two domains in M1 have been shown to affect the disposition of RNA. One domain residing in a palindromic stretch of basic amino acids (101RKLKR105) has been shown to bind vRNA" (Ye 7467, col. 2).

14. Gonzalez is cited to evidence that the influenza PB1 protein specifically binds to the viral RNA, teaching: "Both PB1 and PB2 subunits of the virion core could be cross-linked to the 39-terminal sequence of the

vRNA, and all three subunits were cross-linked to the vRNA 59-terminal sequence" (Gonzalez 631, col. 2; citations omitted).

15. Gonzalez teaches "we show that PB1 protein on its own binds preferentially the 59-terminal sequence of vRNA" (Gonzalez 636, col. 2).

Principles of Law

> [I]t is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. . . . Whether the rejection is based on "inherency" under 35 U.S.C. § 102, on "prima facie obviousness" under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. [Citation omitted].

In re Best, 562 F.2d 1252, 1254-55 (CCPA 1977) (footnote omitted);

Analysis

We begin our analysis with claim construction. We construe each of the structural elements required by claim 1.

"shell"

The Specification states "the term 'shell protein' is defined herein to mean any protein or set of proteins capable of self-assembly or directed-assembly to form a 'shell' of a capsule . . . shell proteins may be either viral or non-viral" (Spec. 40:26–30). We therefore interpret the term "shell" and

"shell protein" as encompassing viral proteins, such as the M1 protein of influenza virus, that self-assemble into virion particles (FF 12).

"cargo protein"

The Specification states "the term 'cargo protein' is defined herein to mean any recombinant protein capable of being incorporated into a synthetic capsule construct" (Spec. 42:1–3). We therefore interpret the term "cargo protein" as encompassing any recombinant protein, including the mutated and recombinant PB1 protein of Perez (FF 10) that is assembled into recombinant virus (FF 11) that inherently comprises both the viral RNA polynucleotide and the PB1 protein (FF 12).

"bifunctional polynucleotide"

The Specification states "the term 'bifunctional polynucleotide' is defined herein to mean a polynucleotide having two or more aptameric activities" (Spec. 41:20–22). As already discussed, the Specification defines an "aptamer" as "an oligonucleotide having binding affinity . . . for a protein tag or a protein binding site" (Spec. 39:23–25).

As applied to claim 1, the bifunctional polynucleotide must be capable of having two binding affinities, one for the cargo protein and one for the shell protein. An additional requirement of claim 1 is that the bifunctional nucleotide is "non-naturally occurring."

Prior art

Perez teaches a recombinant influenza virus particle construct (FF 10–11) that inherently comprises the M1 shell protein (FF 12), PB1 as a "cargo protein" where PB1 is recombinant due to the presence of engineered mutations (FF 11), and bifunctional polynucleotides including the eight viral

RNA segments, one of which is the viral RNA polynucleotide encoding PB1 (FF 12).

Based on the claim interpretation above, we find that the influenza virus M1 protein reasonably satisfies the requirement for the "shell" proteins forming a shell of a capsule construct. We find the mutated and recombinant PB1 protein reasonably satisfies the requirement for a "cargo" protein.

We also find that the vRNA encoding the mutant PB1 inherently satisfies the requirements for the "bifunctional polynucleotide." This vRNA, which is inherently incorporated into the influenza virus particle (FF 12), is non-naturally occurring because it contains mutations in the PB1 nucleic acid sequence that were "engineered" by Perez (FF 10).

In addition, the influenza vRNA polynucleotide inherently is capable of binding to both the M1 shell protein (FF 13) and to the PB1 protein (FF 14–15) noncovalently, inherently satisfying the requirement of the bifunctional polynucleotide of claim 1 to have an aptameric, or "protein binding site" activity for the "shell" protein and for the "cargo" protein (FF 13–15).

We therefore conclude that the influenza virus particles of Perez with mutated PB1 protein and vRNA inherently anticipate the requirements of claim 1.

With regard to claims 2 and 31, the PB1 protein of Perez is a polymerase enzyme involved in virus transcription and replication (FF 10).

With regard to claims 5, 33, and 34, the M1 shell protein is a viral capsid protein (FF 12).

With regard to claims 7 and 35, the M1 shell protein is derived from influenza virus, a single stranded RNA virus (FF12).

With regard to claim 13, the bifunctional polynucleotide is an RNA (FF 10–12).

With regard to claims 14 and 38, the bifunctional polynucleotide is transcribed RNA from a viral genome (FF 12).

With regard to claim 15, the M1 shell protein has a binding site for the vRNA polynucleotide (FF 13).

SUMMARY

In summary, we reverse the rejections of claims 1–5, 7, 8, 11–18, 31–33, 35, and 38 under 35 U.S.C. § 102(b) as anticipated by Young; of claims 1–3, 5, 7, 8, 13–18, and 31–36 under 35 U.S.C. § 103(a) as obvious over Young and Brown; and of claims 1, 5, and 6 under 35 U.S.C. § 103(a) as obvious over Young, Brown, Lim, and Spingola.

We enter a new ground of rejection of claims 1, 2, 5, 7, 13–15, 31, 33–35, and 38 under 35 U.S.C. § 102(b) as anticipated by Perez as evidenced by Mair, Ye, and Gonzalez.

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). Section 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review." Section 41.50(b) also provides:

> When the Board enters such a non-final decision, the appellant, within two months from the date of the decision, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal

> as to the rejected claims:
> (1) Reopen prosecution. Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner. The new ground of rejection is binding upon the examiner unless an amendment or new Evidence not previously of Record is made which, in the opinion of the examiner, overcomes the new ground of rejection designated in the decision. Should the examiner reject the claims, appellant may again appeal to the Board pursuant to this subpart.
> (2) Request rehearing. Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or overlooked in entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

Further guidance on responding to a new ground of rejection can be found in the Manual of Patent Examining Procedure § 1214.01.

<u>REVERSED; 37 C.F.R. § 41.50(b)</u>