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| EXAMINER | |
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| LIU, SAMUEL W | |

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* MARTHA S. HAYDEN-LEDBETTER and JEFFREY A. LEDBETTER

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Appeal 2021-000946
Application 15/909,314
Technology Center 1600

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Before DONALD E. ADAMS, ULRIKE W. JENKS, and JAMIE T. WISZ, *Administrative Patent Judges*.

WISZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 1–13, 16, 22–24, and 27. 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 Theripion, Inc. as the real party-in-interest. Appeal Br. 3.

## CLAIMED SUBJECT MATTER

The Specification describes how low levels of high density lipoprotein (HDL) is associated with increased risk of myocardial infarction. Spec. ¶ 4. Apolipoprotein A-1 (ApoA-1 or ApoA1) is the principal protein component of HDL and has become the focus of several HDL-targeted therapeutic strategies. *Id.* at ¶ 6. The Specification describes compositions and methods relating to ApoA-1 fusion polypeptides comprising ApoA1-L1-D, wherein ApoA-1 is a first polypeptide having cholesterol efflux activity, L1 is a polypeptide linker, and D is an immunoglobulin Fc region. *Id.* at ¶¶ 35–37, 305.

Independent claim 1 is illustrative of the claimed subject matter and is reproduced below:

> 1. A fusion polypeptide comprising, from an amino-terminal position to a carboxyl-terminal position, ApoA1-L1-D, wherein:
>
> ApoA1 is a first polypeptide segment comprising an amino acid sequence having at least 95% identity with amino acid residues 19-267 or 25-267 of SEQ ID NO:2, wherein said first polypeptide segment has cholesterol efflux activity;
>
> L1 is a first polypeptide linker consisting of from 10 to 40 amino acid residues; and D is an immunoglobulin Fc region,
>
> wherein the fusion polypeptide has increased cholesterol efflux activity as compared to the ApoA1-L1-D fusion polypeptide in which L1 is a two amino acid linker or is absent.

Appeal Br. 32 (Claims App.).

## REJECTION

The Examiner rejected claims 1–13 and 27 under 35 U.S.C. § 103 as being unpatentable over Knudsen,[2] Benoit,[3] Igawa,[4] Ledbetter,[5] Heusser,[6] Nezu,[7] Bacus,[8] and Lagerstedt,[9] as evidenced by Wu.[10]

The Examiner rejected claims 16 and 22–24 under 35 U.S.C. § 103 as being unpatentable over Knudsen, Benoit, Igawa, Bacus, Lagerstedt, Heusser, and Nezu, and further in view of Bielicki '632,[11] Rosenblatt,[12] and Bielicki '532.[13]

## ISSUES AND ANALYSIS

*Rejection of claims 1–13 and 27 under 35 U.S.C. § 103 as being unpatentable over Knudsen, Benoit, Igawa, Ledbetter, Heusser, Nezu, Bacus, and Lagerstedt, as evidenced by Wu*

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[2] Knudsen et al., US 2011/0178029 A1, published Jul. 21, 2011 ("Knudsen").
[3] Benoit et al., US 6,258,596 B1, issued Jul. 10, 2001 ("Benoit").
[4] Igawa et al., US 2014/0363428 A1, published Dec. 11, 2014 ("Igawa").
[5] Ledbetter et al., US 8,937,157 B2, issued Jan. 20, 2015 ("Ledbetter").
[6] Heusser et al., US 2012/0121585 A1, published May 17, 2012 ("Heusser").
[7] Nezu et al., US 2014/0112914 A1, published Apr. 24, 2014 ("Nezu").
[8] Bacus et al., US 2009/0318346 A1, published Dec. 24, 2009 ("Bacus").
[9] Lagerstedt et al., US 2015/0353626 A1, published Dec. 10, 2015 ("Lagerstedt").
[10] Wu et al., US 2003/0049694 A1, published Mar. 13, 2003 ("Wu").
[11] Bielicki et al., US 2006/0286632 A1, published Dec. 21, 2006 ("Bielocki '632").
[12] Rosenblat et al., "Paraoxonose 1 (PON1) enhances HDL-mediated macrophage cholesterol efflux via the ABCA1 transporter in association with increased HDL binding to the cells: a possible role for lysophophatidylcholine," Artherosclerosis 179 (2005) 69–77 ("Rosenblat").
[13] Bielicki et al., US 2005/0202532 A1, published Sep. 15, 2005 ("Bielicki '532).

The Examiner finds that Knudsen teaches a fusion protein wherein human Apo-A1 is fused at the N-terminus of the Fc portion of an immunoglobulin by a peptide linker. Final Act. 3–4 (citing Knudsen ¶¶ 13, 68, 674–675, 678). Thus, according to the Examiner, Knudsen teaches the claimed "ApoA1-L1-D" wherein "L1" is a peptide linker and "D" is the Fc region. *Id.* at 4. The Examiner also finds that Knudsen teaches that ApoA-1 promotes cholesterol efflux. *Id.* (citing Knudsen ¶ 737). The Examiner acknowledges that Knudsen does not expressly teach the human ApoA-1 amino acid sequence having at least 95% sequence identity to amino acid residues 19–267 of SEQ ID NO: 2 nor a peptide linker consisting of 10 to 40 amino acids but finds that these limitations are taught by other references. *Id.*

The Examiner finds that Benoit teaches that the gene for human ApoA-1, which is responsible for plasma cholesterol (i.e., cholesterol efflux), has been cloned. *Id.* at 4 (citing Benoit :14–29, 1:49–54). The Examiner further finds that this gene encodes the amino acid sequence of SEQ ID NO: 2 for human ApoA-1. *Id.* at 4–5 (showing how amino acid residues 19–267 of Benoit have 100% sequence identity to amino acid residues 19–267 of SEQ ID NO: 2).

The Examiner finds that Lagerstedt teaches that the ApoA-1 peptide can be fused to the Fc fragment of a mammalian antibody, wherein the fused ApoA-1 peptide has increased plasma half-life as compared to the non-fused peptide. *Id.* at 5 (citing Lagerstedt ¶¶ 261, 264–266). The Examiner also finds that Lagerstedt discloses that the ApoA-1 fusion peptide can include a peptide linker of 10–50 amino acids, wherein said peptide linker codon is made up of a majority of amino acids that are sterically unhindered residues

such as glycine residues, which suggests that a peptide linker with glycine would be suitable for the fusion of ApoA-1 with an Fc peptide. *Id.* (citing Lagerstedt ¶¶ 265–266).

According to the Examiner, Bacus teaches that $Gly_4Ser_3$, which is a glycine rich peptide linker and is non-immunogenic, is a useful linker for fusion proteins. *Id.* (citing Bacus ¶ 31, 52). The Examiner also finds that Bacus teaches that ApoA-1 and Fc peptides can be fusion partners, "suggesting that the peptide linker '$(Gly_4Ser_3)$' is suitable for making fusion protein comprising ApoA-1 and Fc." *Id.* (citing Bacus ¶ 33) (emphasis omitted). The Examiner also finds that Ledbetter discloses the $Gly_4Ser_3$ and $Gly_4Ser_4$ peptide linkers for fusion to the N-terminus of an Fc domain, wherein use of the $Gly_4Ser_4$ linker increased the biological activity of the Fc-containing fusion protein. Ans. 4 (citing Ledbetter 29:26–27, 30:51–58, 32:46–47, 55:45–52, Fig. 11b).

The Examiner concludes that it would have been obvious to one of ordinary skill in the art before the filing date of the invention to use human ApoA-1 to make a fusion protein comprising an Fc peptide and a peptide linker of 10 to 40 amino acid residues because the sequence was known to be responsible for plasma cholesterol (i.e., cholesterol efflux) and it was known that the Fc portion in the fusion protein increases the plasma half-life of the fused ApoA-1. Final Act. 6. According to the Examiner, the suggestion to use a peptide linker with sterically unhindered amino acids such as glycine for the fusion of ApoA-1 is found in Lagerstedt and, in searching for a glycine-rich peptide linker, one of ordinary skill would have found the $Gly_4Ser_3$ linker of Bacus, which describes this linker as being non-immunogenic. *Id.* (citing Bacus ¶¶ 31, 33). The Examiner finds that,

because the $Gly_4Ser_3$ linker is substantially identical in structure to the claimed linker, the increased ApoA-1 calcium efflux activity of the fusion peptide is necessarily present. *Id.* at 7. Thus, the Examiner finds that one of ordinary skill in the art would have constructed the fusion protein which comprises ApoA-1, a peptide linker such as $Gly_4Ser_3$, and an Fc portion of an immunoglobulin, in order to treat disorders such as cardiovascular disease and atherosclerosis with a reasonable expectation of success. *Id.*

Appellant argues that the Examiner has not identified a reason that would have prompted a person of ordinary skill in the art to select an extended linker to join Apo-A1 to the N-terminus of Fc. Appeal Br. 6–21. Appellant also argues that the Examiner did not properly consider evidence of unexpected results. *Id.* at 21–31.

Appellant first asserts that the Examiner has not pointed to any teachings in the art that would suggest the desirability of using an extended linker of at least 10 amino acids to fuse ApoA1 to the N-terminus of an Fc region of an immunoglobulin and that the art fails to teach or suggest any functional relationship between linker length and protein function in the context of an ApoA1-Fc fusion. *Id.* at 8. Appellant also argues that the teachings in the art relied on by the Examiner to prove motivation to use an extended linker are considerations that would arise only after a skilled artisan had already determined that a peptide linker may be needed or desired for joining ApoA1 and Fc. *Id.*

We find that the Examiner has the better position. Knudsen teaches a fusion protein wherein human Apo-A1 is fused to the N-terminus of the Fc portion of an immunoglobulin and discloses that such fusion may be done using a peptide linker. Knudsen ¶¶ 13, 68, 674–675, 678. Thus, Knudsen

teaches that peptide linkers can be used for these fusion proteins and Appellant's argument that one of skill in the art would not have been motivated to use peptide linkers is not persuasive. Further, Lagerstedt teaches that the ApoA-1 peptide can be fused to the Fc fragment of a mammalian antibody using a peptide linker of 10–50 amino acids, wherein the majority of amino acids of the linker are sterically unhindered residues such as glycine residues. Lagerstedt ¶¶ 264–266. Similarly, Bacus teaches that the $Gly_4Ser_3$ peptide linker is useful for fusion proteins, including ApoA-1 and Fc (Bacus ¶¶ 31, 33, 52), and Ledbetter teaches the use of a similar linker ($Gly_4Ser_4$) for a Fc fusion protein and also teaches that incorporation of such a linker increases biological activity of the fusion partner. *See* Ledbetter 55:39–59, Fig. 11b. Based on these teachings, we find that the Examiner has established a *prima facie* case of obviousness because one of ordinary skill in the art would have been motivated to include a linker from 10 to 40 amino acids (such as the $Gly_4Ser_4$ linker) in the fusion peptide taught in Knudsen and would have done so with reasonable expectation of success in increasing biological activity (i.e., increased cholesterol efflux activity), as taught in Ledbetter.

Appellant argues that Knudsen does not provide any guidance that would specifically lead an ordinarily skilled artisan to select a peptide linker of at least 10 amino acid residues. Appeal Br. 9 (citing Oct. 4, 2018 Declaration of Jeffrey A. Ledbetter under 37 C.F.R. § 1.132 ¶ 9 ("Ledbetter Declaration")). However, as discussed above, this teaching is supplied by the other cited references (e.g., Lagerstedt, Bacus, Ledbetter). "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of

references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Appellant also makes arguments regarding the disclosures of Bacus and Ledbetter but, similarly, argues the references individually rather than discussing the prior art in combination. *See* Appeal Br. 11–12, 17–18.

Appellant also asserts that "although Lagerstedt discusses linking or fusing the ApoAl-derived peptide to another molecule such as albumin, a fatty acid, or an Fc fragment," it "does not point to or otherwise suggest any particular reason to use a peptide linker of 10 or more amino acid residues over a shorter linker or no linker when fusing the ApoAl-derived peptide to an Fc fragment." Appeal Br. 10 (citing Lagerstedt ¶ 261; Oct. 20, 2019 Third Declaration of Jeffrey A. Ledbetter under 37 C.F.R. § 1.132 ¶ 9 ("Third Ledbetter Declaration")). According to Appellant, Lagerstedt does not include any functional data for an ApoA-1-derived peptide linked to an Fc region and no such data using longer linkers. *Id.* As discussed above, Lagerstedt teaches use of a 10–50 amino acid linker in ApoA1-Fc fragment fusion peptides and the disclosures of Bacus and Ledbetter further support this disclosure. The fact that Lagerstedt does not include examples or data of this embodiment does not negate its disclosure. "[I]n a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'" *Merck & Co. Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)).

Appellant further contends that the Examiner did not properly consider evidence of unexpected results. Appeal Br. 21. Appellant points to Example 1 of the Specification which describes a study that compared the activity of an ApoA1-Fc protein without a linker with that of ApoA1-Fc fusions containing either a 2 amino acid linker or a 26 amino acid linker between ApoA-1 and the Fc region. *Id.* at 22; Spec. ¶ 248, Fig. 1. According to Appellant, the results of the study showed that cholesterol efflux was significantly increased in cultures containing ApoA1-Fc with the 26 amino acid linker compared to either ApoA1-Fc with the 2 amino acid linker or without a linker. *Id.* at 22–23 (citing May 23, 2019 Second Declaration of Jeffrey A. Ledbetter under 37 C.F.R. § 1.132 ¶ 9 ("Second Ledbetter Declaration")).

Appellant also presents the results of a separate cholesterol efflux study in which the activity of six different ApoA1-Fc molecules with linkers of either 2, 5, 10, 16, 26, or 36 amino acids in length, were compared. *Id.* at 23 (citing Second Ledbetter Declaration ¶17). According to Appellant, cholesterol efflux activity of the fusion polypeptides having 10, 16, 26, or 36 amino acid linkers was substantially increased relative to ApoA1-Fc fusion polypeptides having a 2 amino acid linker. *Id.* (citing Second Ledbetter Declaration ¶ 19, Exhibit C). Appellant states that the molecule with a 5 amino acid linker also had significantly more efflux activity than the molecule with a 2 amino acid linker, although not as much as the polypeptides with linkers of 10 or more amino acids. *Id.* Appellant asserts that these results of superior performance could not have been predicted by an ordinarily skilled artisan from the cited prior art. *Id.*

We are not persuaded that Appellant has provided evidence of unexpected results that, considered with the *prima facie* case, supports a finding of non-obviousness. As discussed above, Bacus teaches that the $Gly_4Ser_3$ peptide linker is useful for fusion proteins, including ApoA-1 and Fc (Bacus ¶¶ 31, 33, 52), and Ledbetter teaches that incorporation of a similar linker ($Gly_4Ser_4$) in a Fc fusion protein increased the biological activity of the fusion partner. *See* Ledbetter 55:39–59; Fig. 11b. Specifically, Ledbetter compares the biological activity of a Fc fusion protein with a $Gly_4Ser_4$ peptide linker to the activity of a fusion protein lacking this linker and finds that the incorporation of the linker increases the biological activity of the fusion partner (a nuclease) compared to the protein lacking the linker. *See id.* Ledbetter also teaches that the linker length was critical in creating a highly active DNase enzyme in the context of the bispecific nuclease Fc fusion protein. *Id.* at 55:58. Thus, one of ordinary skill in the art would similarly expect that use of a peptide linker, such as $Gly_4Ser_4$, would increase the biological activity (i.e., cholesterol efflux activity) of a Fc fusion protein with ApoA1. "Scientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention." *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1363 (Fed. Cir. 2007).

Therefore, we affirm the Examiner's rejection of claim 1 as being unpatentable over Knudsen, Benoit, Igawa, Ledbetter, Heusser, Nezu, Bacus, and Lagerstedt, as evidenced by Wu. Claims 2–13 and 27 are not argued separately apart from the independent claim, and, therefore, fall with claim 1. *See* 37 C.F.R. § 41.37(c)(1)(iv).

*Rejection of claims 16 and 22–24 under 35 U.S.C. § 103 as being unpatentable over Knudsen, Benoit, Igawa, Bacus, Lagerstedt, Heusser, Nezu, and further in view of Bielicki '632, Rosenblatt, and Bielicki '532*

Appellant did not separately argue the Examiner's rejection of claims 16 and 22–24. Thus, for the same reasons as discussed above, we affirm the Examiner's rejection of these claims.

## CONCLUSION

For the reasons described herein and those already of record, we affirm the Examiner's rejection of claims 1–13, 16, 22–24, and 27.

## DECISION SUMMARY

In summary:

| Claim(s) Rejected | 35 U.S.C. § | Reference(s)/Basis | Affirmed | Reversed |
|---|---|---|---|---|
| 1–13, 27 | 103(a) | Knudsen, Benoit, Igawa, Ledbetter, Heusser, Nezu, Bacus, Lagerstedt, Wu | 1–13, 27 | |
| 16, 22–24 | 103(a) | Knudsen, Benoit, Igawa, Bacus, Lagerstedt, Heusser, Nezu, Bielicki '632, Rosenblatt, Bielicki '532 | 16, 22–24 | |
| **Overall Outcome** | | | 1–13, 16, 22–24, 27 | |

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

AFFIRMED