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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte JEAN C.Y. WANG, JOHN DICK, JAYNE DANSKA, LIQING JIN, ALEXANDRE THEOCHARIDES, and SUJEETHA RAJAKUMAR

_____

Appeal 2019-006491
Application[1] 13/320,629
Technology Center 1600

_____

Before FRANCISCO C. PRATS, ULRIKE W. JENKS, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for treating a patient having cancer cells or tumours that are $CD47^{+}$, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

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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 University Health Network, The Hospital for Sick Children, and Trillium Therapeutics, Inc. (Appeal Br. 2.)

STATEMENT OF THE CASE

According to Appellant's Specification it is known that "CD47 is expressed in most human AML [(acute myeloid leukemia)] samples." (Spec. 2.) "CD47 is [also] present on most hematopoietic cells." (*Id.* at 1.) "CD47 expression is higher on human AML LSCs [(human leukemia initiating cells)] compared to normal HSCs [(hematopoietic stem cells)]." (*Id.* at 2.) However, "little is known about molecular regulators that govern AML-LSC fate." (*Id.*)

Appellant's Specification states that "[t]reatment of immune-deficient mice engrafted with human AML with a monoclonal antibody directed against CD47 results in reduction of leukemic engraftment in the murine bone marrow." (*Id.*)

"In mouse and human, Sirpa encodes for the SIRPα protein which interacts with its ligand CD47. In the hematopoietic system, SIRPα is mainly found on macrophages, dendritic cells, and granulocytes." (Spec. 1.) Appellant's "invention relates to targeting the SIRPα–CD47 interaction in order to treat hematological cancer, particularly human acute myeloid leukemia." (*Id.*)

Claims 1, 3, 4, 7, 9–12, 32, and 54–86 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method for treating a patient having cancer cells or tumours that are $CD47^{+}$, comprising administering to the patient a therapeutically effective amount of a fusion protein capable of binding to the extracellular domain of human CD47 to interrupt signaling between human Sirpα and human CD47, wherein the fusion protein comprises a first polypeptide comprising soluble human Sirpα, or a CD47 binding fragment thereof, fused to a second polypeptide comprising the Fc

> portion of IgG, and wherein the method results in a desuppression of macrophages.

(Appeal Br. 34.)

The prior art relied upon by the Examiner is:

Name	Reference	Date
Jamieson et al.	US 2009/0191202 A1	July 30, 2009
Smith et al.	US 2010/0239579 A1	Sept. 23, 2010
Danska et al.	US 2010/0239578 A1	Sept. 23, 2010
Yuan Liu et al., *Functional Elements on SIRPα IgV domain Mediate Cell Surface Binding to CD47*, 365(3) J. Mol. Biol. 680–93 (2007)		

The following ground of rejection by the Examiner is before us on review:

Claims 1, 3, 4, 7, 9–12, 32, and 54–86 under 35 U.S.C. § 103(a) as unpatentable over Liu,[2] Smith, Jamieson, and Danska.

DISCUSSION

The Examiner finds that "Liu teaches contacting promyelocytic leukemic cell line, HL-60 with wild-type and mutant soluble SIRPα1.IgV-Fc fusion proteins," as well as contacting CD47 expressing epithelial cells with SIRPα-IgV-Fc fusion proteins. (Ans. 3; Final Action 7.) The Examiner additionally finds that "HL-60 promyelocytic leukemic cells are art known to express CD47." (*Id.*)

The Examiner finds that Smith teaches a fusion polypeptide that includes the CD47 extracellular domain fused to an Fc polypeptide that is used to treat proliferative orders such as B-cell chronic lymphocytic

[2] The Examiner relies on the "Author Manuscript" of Liu which is paginated 1–27. We likewise refer to this Author Manuscript.

leukemia and lymphoma where the Fc portion can include IgG1 or IgG4. (Ans. 3–4; Final Action 8.)

The Examiner finds that Jamieson teaches CD47 expression is present in acute myeloid leukemia (AML) and diffuse large B-cell lymphoma (DLBCL), known as a B-cell non-Hodgkin's lymphoma, and that using molecules that disrupt the CD47-SIRPα interaction, represses CD47 on the tumor cells, allows for phagocytosis of them by macrophages and clearing of those cells. (Ans. 4; Final Action 8.)

The Examiner finds that Danska teaches 3 particular polypeptides that are "capable of interrupting signaling between SIRPα and CD47" and explains that those polypeptides are the same as Appellant's SEQ ID NOs: 4, 6, and 7. (Ans. 4; Final Action 8.)

> The Examiner concludes that in view of Jamieson's teaching that
>
> SIRPα1.IgV-Fc fusion proteins are able to mediate cell surface binding to CD47 and with the implementation of molecules able to disrupt the CD47-SIRPα interaction there is consequent repression of CD47, phagocytosis and clearing of tumor cells by macrophages

it would have been obvious to one having ordinary skill in the art "to treat additional CD47 expressing cells [beyond those described in Liu] with fusion polypeptides that comprise SIRPα extracellular domain or variant thereof that is fused to a Fc polypeptide and/or a CD47-binding fragment." (Ans. 4.)

We agree with the Examiner that the cited prior art renders the claimed invention prima facie obvious. In particular, Appellant does not dispute that Jamieson teaches targeting tumor cells or leukemia cells for phagocytosis using CD47 monoclonal antibodies. (Appeal Br. 19.) Although Jamieson exemplifies the use of CD47 monoclonal antibodies,

Jamieson's teachings suggest extension to other compounds that prevent interaction between CD47 on the cancer cell and SIRPα.

Jamieson explains "tumor cells, e.g. solid tumor cells, leukemia cells, etc. are targeted for phagocytosis by blocking CD47 on the cell surface." (Jamieson ¶ 13.) Jamieson indicates that they tested "the model that CD47 overexpression on AML LSC prevents phagocytosis of these cells through its interaction with SIRPα on effector cells" with a "monoclonal antibody directed against CD47 known to disrupt the CD47-SIRPα interaction." (*Id.* ¶ 131.) "[S]ignificant phagocytosis was detected with the addition of the anti-CD47 antibody (FIG. 9). Thus, blockage of human CD47 with a monoclonal antibody is capable of stimulating the phagocytosis of these cells by mouse macrophages." (*Id.*) Jamieson further states that "[f]inding methods to disrupt CD47-SIRPα interaction may thus prove broadly useful in developing novel therapies for cancer." (*Id.* ¶ 146.) Thus, we conclude that Jamieson suggests that "agents that mask the CD47 protein" by binding to CD47 so as to "prevent interaction between CD47 and SIRPα" will likely increase the clearance of AML cells via phagocytosis, which cells are otherwise able to "evade macrophage surveillance by upregulation of CD47 expression." (*See, e.g.*, *id.* ¶ 13.)

As Appellant acknowledges, Liu teaches SIRPα constructs. (Appeal Br. 8.) Liu's teachings go beyond that simple fact, however. Liu identifies seven amino acids on SIRPα that are "unique" compared to SIRPβ, a protein that is "commonly co-expressed on the same cell surfaces of neutrophils and mononuclear cells" as SIRPα and shares a "strikingly similar extracellular domain structure[] with highly homologous amino acid sequences" but does not bind to CD47, which amino acids "likely form a functional motif on

SIRPα protein surface that mediates specific binding interaction with CD47." (Liu 1, 6–7.) Liu states that: "Our results thus revealed the molecular basis by which SIRPα selectively binds to CD47." (*Id.* at 1.)

Liu "generated SIRPαl.IgV-Fc and Bit.IgV-Fc fusion proteins[3]" that were "tested for binding to CD47 using CD47 extracellular domain fusion protein, CD47-AP."[4] (Liu 3.) Both fusion proteins "directly bound to CD47-AP and exhibited equivalent binding capability." (*Id.*) In addition, as the Examiner noted, these fusion proteins were determined to bind to HL-60 cells. (*Id.* at 5.) Appellant does not dispute the Examiner's finding that "HL-60 promyelocytic leukemic cells are art known to express CD47." (Ans. 3; Final Action 7.)

Furthermore, although we agree with Appellant that Smith "teaches a **different molecule** than the present inventors, to treat a **different class of disease**" (Appeal Br. 14), Smith, nevertheless, teaches uses of "[a]n Fc polypeptide or portion thereof (such as at least one immunogloblulin constant region domain, for example, the CH2 domain or CH3 domain) when fused to a peptide or polypeptide of interest" for *in vivo* therapeutic use. (Smith ¶ 48.) In particular, Smith states the Fc portion of the fusion peptide

> acts, at least in part, as a vehicle or carrier moiety that prevents degradation and/or increases half-life, reduces toxicity, reduces immunogenicity, and/or increases biological activity of the peptide such as by forming dimers or other multimers

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[3] Liu explains that "SIRPα subfamily contains multiple members, such as Bit, SIRP αl and α2, which vary mainly in the membrane-distal IgV domains." (Liu at 3.)

[4] AP is alkaline phosphatase. (*Id.* at 14.)

(*Id.*)

In light of these teachings, we agree with the Examiner that it would have been prima facie obvious to use the fusion protein described by Liu in targeting tumor cells or leukemia cells for phagocytosis as taught in Jamieson with a reasonable expectation of success. We do not find Appellant's argument to the contrary (Appeal Br. 10, 26) persuasive. That "most of the cited prior art - including all of the cited art relating to fusion constructs - demonstrated or hypothesized that interference with the S1RPα/CD47 signalling pathway had a suppressive effect on various components of the immune system" (*id.*) does not negate Jamieson's clear suggestion that a compound that specifically binds to the external cellular domain of CD47 and prevents the interaction between CD47 and SIRPα will be reasonably likely to at least increase the clearance of AML cells via phagocytosis, which cells would have otherwise evaded macrophage surveillance by upregulation of CD47 suppression. That Jamieson's experimental evidence employed an antibody that was specific for the extracellular domain of CD47 and not to a SIRPα-Fc construct (*see, e.g.*, Appeal Br. 26 (emphasis omitted) ("No direct evidence in the cited prior art that soluble Sirpα-Fc has anti-cancer activity")) is immaterial, as such evidence is not necessary to establish a reasonable expectation of success where the art indicates other compounds that can prevent the interaction between CD47 and SIRPα would be expected to achieve the same result. (Jamieson ¶¶ 13, 145–146.)

That the treatment "was not yet established in the field" (Appeal Br. 10) does not defeat obviousness. "Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness." *In*

re Longi, 759 F.2d 887, 897 (Fed. Cir. 1985). Appellant's claim requires that the method of treatment results in desuppression of macrophages. Jamieson's teachings combined with the fact that Liu teaches a fusion protein construct of SIRPα that specifically binds to CD47 on the cell surface of a leukemic cell line provides the reasonable expectation of success.

We have considered the Declaration of Dr. Uger[5] (Appeal Br. 25) in arriving at our conclusion. We appreciate the following statements by Dr. Uger

> First, at the time of the patent application in 2009, a number of lines of evidence had been reported implicating macrophages in tumor progression. In view of this evidence, there was a basis for concluding that suppression or depletion of tumor associated macrophages was the proper approach to enhancing cancer therapy. Stated differently, there was no consensus that de-suppression of macrophages was the desirable approach to cancer therapy.
>
> Second, the evidence relating to macrophages and cancers was focused on a number of signaling molecules and cellular functions other than the CD47-Sirpα "do not eat" signaling that is the focus of the patent application.
>
> A potential complication of therapies designed to target CD47 on cancer cells to suppress a "do not eat" signal is the fact that CD47 also is expressed on many healthy cells throughout the body, including on the surface of red blood cells (RBCs).

(Uger Declaration ¶¶ 3.8–3.9, 4.1 (emphasis omitted).) However, Dr. Uger does not address Jamieson and its teachings, which strongly implicate that other compounds besides antibodies that specifically bind to the external cellular domain of CD47 and prevent the interaction between CD47 and

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[5] Declaration of Robert Uger, PhD. dated January 15, 2018.

SIRPα will be reasonably likely to at least increase the clearance of AML cells via phagocytosis, in the Declaration. Thus, we do not find Appellant's argument that

> The Rule 132 Declaration of Dr. Uger explains that it was uncertain, at the time of the invention, that therapies targeted at potentiating macrophages would be successful for the treatment of cancer because substantial scientific literature existed which had reported that macrophages appear to play a role in cancer progression

(Appeal Br. 25) (emphasis omitted), persuasive that the Examiner's evidence does not establish a prima facie case of obviousness.

Appellant's argument that "a person of ordinary skill would not and could not have extrapolated, with a reasonable expectation of success, that results reportedly obtained with CD47 antibodies would be predictive of results with soluble Sirpα-Fc" given "[t]he complexity of CD47 biology" and because the CD47 antibodies of Jamieson "are a different size than Sirpα-Fc, potentially bind to different CD47 epitopes than Sirpα-Fc, and do not necessarily bind with the same affinity" (Appeal Br. 29) is not persuasive. First, we note this argument is not supported by any declaration testimony. "Attorneys' argument is no substitute for evidence." *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989). Second, Liu teaches specific binding of soluble Sirpα-Fc to cell bound CD47 on a leukemic cell line and determines the seven amino acids that are important for such binding. It is true as Appellant notes that Liu teaches "soluble Sirpα 'demonstrated remarkable binding/adhesion' to healthy PBMC and RBC" (Appeal Br. 29). However, Liu teaches that differentiated HL-60 cells "demonstrated remarkable binding/ adhesion" as well. (Liu 4.) In addition, Liu teaches that the greater the number of CD47 on the cell surface of the

leukemic cells (differentiated v. undifferentiated HL60 cells), the better the adhesion of Bit IgV. (*Id.*) The fact of greater binding to RBC than to other tested cell types (Appeal Br. 29) is of little significance for non-obviousness given that the experimental setting was not one in which a multiplicity of cell types was provided in the same well and contacted with the SIRPα-Fc fusion peptide. Appellant suggests that Dr. Uger's Declaration concluded that "the adhesion to healthy cells would have suggested that the treatment could have unacceptable side effects and/or could fail to reach the target cells due to the plentiful RBC population acting as an 'antigen sink.'" (Appeal Br. 29 (citing Uger Declaration ¶¶ 4.1 - 4.3.).) However, Dr. Uger made no such conclusion when also considering the teachings of Jamieson. "Attorney's argument in a brief cannot take the place of evidence." *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974).

Moreover, even considering that CD47 is expressed on the surface of RBCs, Dr. Uger only notes that for "therapies designed to target CD47 on cancer cells to suppress a 'do not eat' signal" this is "[a] potential complication," not that a SIRPα-Fc fusion peptide would fail to reach its cancer target cell and be incapable of desuppressing macrophages.

Notwithstanding the foregoing, we conclude that Appellant has provided evidence of unexpected results in the record that when weighed together with the Examiner's evidence of obviousness is sufficient for us to conclude that the Examiner's ultimate holding of obviousness should not stand. *In re Huai-Hung Kao*, 639 F.3d 1057, 1066 (Fed. Cir. 2011) (citations omitted) ("Once the examiner establishes a prima facie case of obviousness, the burden shifts to the applicant to rebut that case. . . . However, once the applicant has come forward with rebuttal evidence, the

examiner must consider the totality of the evidence to determine whether the obviousness rejection should stand.")

In particular, Appellant presented unrebutted evidence that a Sirpα-Fc fusion construct "displays markedly reduced RBC binding and agglutination compared to anti-CD47 antibodies," including the antibody described in Jamieson, B6H12 (Appeal Br. 11; Jamieson ¶ 23). Dr. Uger discusses the experiments and resultant data in his declaration. (Uger Declaration ¶¶ 5.1–5.6.) Dr. Uger explains that the SIRPα-Fc fusion protein (TTl-621) exhibited only minimal binding to human erythrocytes, compared with high binding of five different anti-CD47 antibody clones. (*Id.* ¶ 5.3 (referring to Figures 1A and 1B).) Figure 1B demonstrating the difference in binding is reproduced below.

Figure 1B

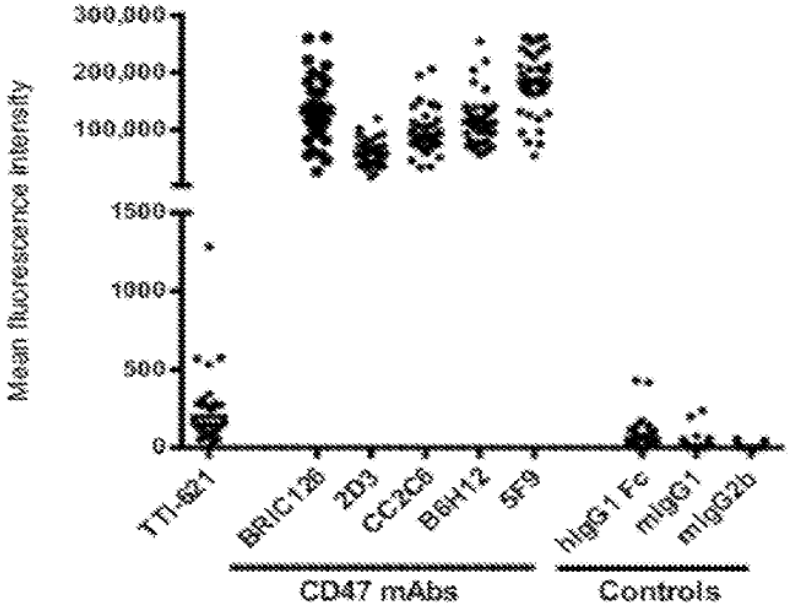

Figure 1B depicts binding of erythrocytes from 43 healthy donors to controls, 5 CD47 monoclonal antibodies included B6H12, and the SIRPα-Fc fusion protein (TTl-621) with mean fluorescence intensity. The difference in intensity is several orders of magnitude between the TTI-621 and all the CD47 monoclonal antibodies tested. Dr. Uger states that the experiments, which included testing of different FC isotypes and different domain structures, which data is not shown, "indicate that SIRPα-Fc fusion proteins bind poorly to human RBCs regardless of Fc isotype . . . and regardless of whether a one-or three-domain structure . . . from the Sirpα extracellular region is used to make the further protein." (*Id.* ¶ 5.4.) Dr. Uger further explains that the difference in erythrocyte binding "does not simply reflect a difference in overall activity: both classes of proteins trigger similar levels of tumor cell phagocytosis." (*Id.* ¶ 5.6.) Although this phagocytic activity was observed using monoclonal antibody 5F9, and not B6H12, we note that, as can be seen in the figure above, the erythrocyte binding of 5F9 and B6H12 were both at least two orders of magnitude higher than TTI-621.

In response to this data, the Examiner states that the "declaration and Exhibits have been carefully considered, but fail to persuade." (Final Action 4; *see also* Ans. 10 ("Appellant[] ha[s] not produced sufficient evidence showing that the determinations herein on obviousness are incorrect or misplaced").) According to the Examiner, "the specific properties achieved are merely inherent properties of the combination" and there is an "absence of adequate evidence of unexpectedly superior results." (Final Action 5.) We do not find the Examiner's response sufficient to discount Appellant's evidence. That evidence demonstrates a substantial difference in a particular property between the prior art compound established in Jamieson to

desuppress macrophages which would necessarily result in lower side effects when the claimed fusion protein is used to treat cancer by desuppressing macrophages. "Given a presumption of similar properties for similar compositions, substantially improved properties are *ipso facto* unexpected." *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995). The Examiner established a prima facie case, the Appellant responded to it with a showing of data, and the Examiner made an inadequate challenge to the adequacy of that showing. *Id.*

The foregoing applies to each of the independent claims in appeal, i.e., claims 1, 9, and 75. For this reason, we do not affirm the Examiner's rejection of claims 1, 3, 4, 7, 9–12, 32, and 54–86 under 35 U.S.C. § 103(a) as unpatentable over Liu, Smith, Jamieson, and Danska.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 3, 4, 7, 9–12, 32, 54–86	103	Liu, Smith, Jamieson, Danska		1, 3, 4, 7, 9–12, 32, 54–86

REVERSED