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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOHN McWHIRTER, LYNN MacDONALD, SEAN STEVENS, SAMUEL DAVIS, DAVID R. BUCKLER, and ANDREW J. MURPHY

Appeal 2016-003721
Application 13/948,818
Technology Center 1600

Before DONALD E. ADAMS, JEFFREY N. FREDMAN, and JOHN G. NEW, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134 involving claims to a mouse that expresses a population of antibodies. The Examiner rejected the claims as obvious and on the ground of provisional obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

Antibodies are "immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds" (Spec. ¶ 68). "Antibodies typically comprise

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[1] Appellants identify the Real Party in Interest as Regeneron Pharmaceuticals, Inc. (*see* App. Br. 2).

a homodimeric heavy chain component, wherein each heavy chain monomer is associated with an identical light chain. Antibodies having a heterodimeric heavy chain component (e.g., bispecific antibodies) are desirable as therapeutic antibodies" (Spec. ¶ 4). "The phrase 'bispecific antibody' includes an antibody capable of selectively binding two or more epitopes" (Spec. ¶ 69). "But making bispecific antibodies having a suitable light chain component that can satisfactorily associate with each of the heavy chains of a bispecific antibody has proved problematic" (Spec. ¶ 4).

"The inventors have engineered a mouse for generating immunoglobulin light chains that will suitably pair with a rather diverse family of heavy chains, including heavy chains whose variable regions depart from germline sequences, *e.g.*, affinity matured or somatically mutated variable regions" (Spec. ¶ 89).

> In order to achieve this, the mouse is engineered to present a limited number of human light chain variable domain options in conjunction with a wide diversity of human heavy chain variable domain options. Upon challenge with an immunogen, the mouse maximizes the number of solutions in its repertoire to develop an antibody to the immunogen, limited largely or solely by the number or light chain options in its repertoire.

(Spec. ¶ 90). "In one aspect, a genetically modified mouse is provided that comprises a single rearranged (V/J) human immunoglobulin light chain variable (VL) region segment (*i.e.*, a V/J segment) that encodes a human VL domain of an immunoglobulin light chain" (Spec. ¶ 17).

The Claims

Claims 1–6 and 9–23 are on appeal. Appellants state that claims 1–6 and 9–23 stand or fall together (*see* App. Br. 6). Claim 1 is representative and reads as follows:

> 1. A mouse that expresses a population of antigen-specific antibodies in response to challenge with an antigen,
>
> wherein all immunoglobulin light chains of the population of antigen-specific antibodies comprise a human immunoglobulin light chain variable region derived from a single rearranged human light chain variable region sequence in a germline of the mouse, wherein the single rearranged human light chain variable region sequence comprises a human germline Vκ1-39 gene segment, wherein at least one of the population of antigen-specific antibodies comprises a light chain that is somatically mutated, and
>
> wherein the population of antigen-specific antibodies comprises a plurality of affinity-matured immunoglobulin heavy chains selected by the mouse, wherein each of the plurality of affinity matured heavy chains comprises a human immunoglobulin heavy chain variable region that pairs with said light chain variable region, wherein the heavy chain variable region comprises a sequence derived from one of a plurality of human V_H segments including at least one of V_H2-5, V_H3-23, V_H3-30, and V_H4-59.

The Issues

A. The Examiner rejected claims 1–6 and 9–23 under 35 U.S.C. § 103(a) as obvious over Lonberg,[2] Murphy,[3] Mendez,[4] and de Wildt[5] (Final Act.[6] 2–6).

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[2] Lonberg et al., US 2006/0015957 A1, published Jan. 19, 2006.
[3] Murphy et al., WO 02/066630 A1, published Aug. 29, 2002.
[4] Michael J. Mendez et al., *Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice*, 15 NATURE GENETICS 146–56 (1997).
[5] Ruud M.T. de Wildt et al., *Analysis of Heavy and Light Chain Pairings Indicates that Receptor Editing Shapes the Human Antibody Repertoire*, 285 J. MOLECULAR BIOL. 895–901 (1999).
[6] We refer to the Final Action mailed Mar. 25, 2015.

B. The Examiner rejected claims 1–6 and 9–23 on the ground of nonstatutory double patenting as being unpatentable over: Claims 1–10, 12, 13, and 15–34 of copending Application No. 13/092, 156; Claims 1–8, 10–17, and 19–21 of copending Application No. 13/022,759; Claims 1, 2, and 4–18 of copending application 13/412,936; and Claims 14–27 of copending Application 13/798,310 (Final Act. 6–7).

A. 35 U.S.C. § 103(a) over Lonberg, Murphy, Mendez, and de Wildt

The Examiner finds that Lonberg teaches

> transgenic mice generated from a transgene construct comprising a rearranged human light chain variable region can be bred with human heavy chain transgenic mice to produce a mouse which expresses a spectrum of antibodies in which the diversity of the primary repertoire is contributed by the unrearranged heavy chain transgene.

(Ans. 6). The Examiner finds Lonberg teaches "the unrearranged human heavy chain transgene comprises several human VH, DH, and JH gene segments" (*id.*).

The Examiner acknowledges Lonberg "does not specifically teach a transgenic mouse comprising a rearranged human light chain transgene" but contends Lonberg

> provides specific motivation for using a rearranged rather than an unrearranged light chain transgene by teaching that the advantage of using a rearranged light chain transgene, as opposed to the use of unrearranged light chain miniloci, is the increased light chain allelic and isotypic exclusion that comes from having the light chain ready to pair with a heavy chain as soon as heavy chain VDJ joining occurs.

(Ans. 7; citing Lonberg ¶ 482).

The Examiner relies on Murphy to demonstrate the technical feasibility of "'knock-in' of the human kappa light chain and/or lambda light chain into the endogenous mouse kappa or lambda light chain variable region respectively" as well as that "human immunoglobulin knock-in mice can be used in methods of making antibodies" (Ans. 8). The Examiner relies on Mendez to demonstrate that a YAC (yeast artificial chromosome) containing human heavy chain V segments, D segments, and J segments "can be successfully inserted into a mouse genome and undergo productive rearrangement" (Ans. 9). The Examiner also relies on Mendez to teach the specific human heavy chain segments V_H2-5, V_H3-23, V_H3-30, and V_H4-59 recited in claim 1 (*id.*).

The Examiner finds de Wildt teaches antibody "diversity is generated both by combinatorial rearrangement of different gene segments and the association of different heavy and light chains which generates a primary repertoire, and by somatic mutation and receptor editing which results in the secondary repertoire" (Ans. 10). The Examiner finds it obvious "to select a germline rearranged human light chain variable region sequence rather than a rearranged sequence that has already undergone somatic hypermutation in response to a specific antigen" (*id.*).

The Examiner relies upon de Wildt to teach "that Vk 02/12 (also known as Vk1-39) is one of the most common human V gene segments found in the human antibody repertoire and is capable of pairing with a large number of different heavy chain variable regions" (Ans. 10). The Examiner finds it obvious to use the Vκ1-39 segment "based on the high frequency of usage of the Vk1-39 variable region gene segment in the human antibody repertoire taught by de Wildt" (Ans. 10–11).

The issue with respect to the rejection is: Does the evidence of record support the Examiner's conclusion that the prior art suggests a mouse with a "single rearranged human light chain variable region sequence comprises a human germline Vκ1-39 gene segment" and "one of V_H2-5, V_H3-23, V_H3-30, and V_H4-59" as required by claim 1?

Findings of Fact

1. Lonberg teaches "transgenic nonhuman animals are provided which are capable of producing a heterologous antibody, such as a human antibody" (Lonberg ¶ 13).

2. Lonberg teaches "to provide heterologous unrearranged and rearranged immunoglobulin heavy and light chain transgenes useful for producing the aforementioned non-human transgenic animals" (Lonberg ¶ 16).

3. Lonberg teaches:

> transgenic animals containing germ line cells having a heavy and light transgene wherein one of the said transgenes contains rearranged gene segments with the other containing unrearranged gene segments. In the preferred embodiments, the rearranged transgene is a light chain immunoglobulin transgene and the unrearranged transgene is a heavy chain immunoglobulin transgene.

(Lonberg ¶ 201).

4. Lonberg teaches a "kappa light chain expression cassette was designed to reconstruct functionally rearranged light chain genes that have been amplified by PCR from human B-cell DNA . . . a reconstructed functionally rearranged kappa light chain transgene that can be excised with NatI for microinjection into embryos" (Lonberg ¶ 481).

5. Lonberg teaches: "Transgenic mice generated with the rearranged light chain constructs can be bred with heavy chain minilocus transgenics to produce a strain of mice that express a spectrum of fully human antibodies in which all of the diversity of the primary repertoire is contributed by the heavy chain" (Lonberg ¶ 482).

6. Lonberg teaches:

> Because not all light chains will be equivalent with respect to their ability to combine with a variety of different heavy chains, different strains of mice, each containing different light chain constructs can be generated and tested. The advantage of this scheme, as opposed to the use of unrearranged light chain miniloci, is the increased light chain allelic and isotypic exclusion that comes from having the light chain ready to pair with a heavy chain as soon as heavy chain VDJ joining occurs. This combination can result in an increased frequency of B-cells expressing fully human antibodies.

(Lonberg ¶ 482).

7. Lonberg teaches "to disrupt endogenous immunoglobulin loci in the transgenic animals" (Lonberg ¶ 17). Lonberg teaches: "There are three ways to disrupt each of these loci, deletion of the J region, deletion of the J-C intron enhancer, and disruption of constant region coding sequences by the introduction of a stop codon" (Lonberg ¶ 296).

8. Lonberg teaches:

> Rearranged light chain transgenes constructs that result in the highest level of human heavy /light chain complexes on the surface of the highest number of B cells, and do not adversely affect the immune cell compartment (as assayed by flow cytometric analysis with B and T cell subset specific antibodies), are selected for the generation of human monoclonal antibodies.

(Lonberg ¶ 553).

9. Lonberg teaches: "Because of the limited diversity generated by simple VJ and VDJ joining, the antibodies produced by the so-called primary response are of relatively low affinity" (Lonberg ¶ 216).

10. Lonberg teaches that "somatic mutation during the secondary-response occurs throughout the V region including the three complementary determining regions" and that "[d]uring hypermutation, the rearranged DNA is mutated to give rise to new clones with altered Ig molecules. Those clones with higher affinities for the foreign antigen are selectively expanded" (Lonberg ¶ 218).

11. Murphy teaches "[t]he use of chimeric antibodies, which utilize human variable regions (VDJ /VJ) with mouse constant regions through B cell maturation, followed by subsequent engineering of the antibodies to replace the mouse constant regions with their human counterparts, has been suggested" (Murphy 42:34 to 43:2).

12. Murphy teaches "murine Fc regions will be more specific than human Fc regions in their interactions with Fc receptors on mouse cells, complement molecules, etc. These interactions are important for a strong and specific immune response, for the proliferation and maturation of B cells, and for the affinity maturation of antibodies" (Murphy 43:34 to 44:3).

13. Mendez teaches "we set out to recapitulate the human antibody response in mice by constructing megabase-sized YACs bearing the majority of the human heavy and κ light chain loci and introducing them into the germline of Ig -inactivated mice" (Mendez 146, col. 2 to 147, col. 1).

14. Figure 1, panel A of Mendez is reproduced below:

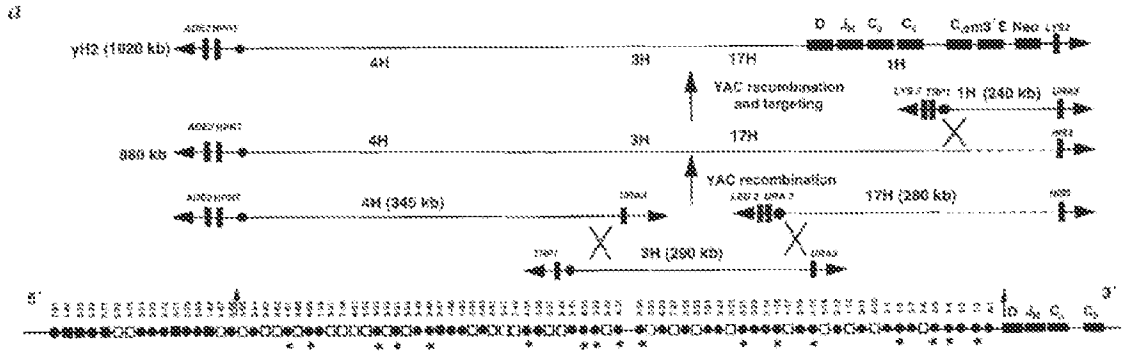

Figure 1a of Mendez illustrates a schematic of a yeast artificial chromosome containing a number of heavy chain segments including V_H2-5, V_H3-23, V_H3-30, and V_H4-59 (Mendez 147, figure 1).

15. Mendez teaches: "Our findings confirm the ability of the introduced human Ig YACs to induce proper *Ig* gene rearrangement and class switching and to generate significant levels of fully human IgM and IgG antibodies before and after immunization" (Mendez 149, col. 2).

16. de Wildt teaches: "Diversity in the primary B cell repertoire is created by the combinatorial rearrangement of different variable (V), diversity (D) and joining (J) gene segments (Tonegawa, 1983), by junctional diversity and by the association of different heavy and light chains. Additional diversity can be created by somatic hypermutation" (de Wildt 895, col. 1).

17. Figure 1 of de Wildt depicts a variety of light chain segments, including Vk1-39 (also known as Vk 02/12) and Vk 3-20 (also known as A27) variable region gene segment function to interact with heavy chain (*see* de Wildt 896, figure 1; *cf.* Ans. 20).

18. de Wildt teaches "receptor editing operates in conjunction with somatic mutation to improve antibody affinities both by removing

undesirable mutations and by creating further diversity" (de Wildt 899, col. 1).

Principles of Law

"[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the [S]pecification." *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000).

"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 (Non-Final Act. 4–10; FF 1–18) and agree that claim 1 is obvious over Lonberg, Murphy, Mendez, and de Wildt. We address Appellants' arguments below.

Appellants contend:

> Prior to the present invention, there simply was no expectation in the art that it would be possible for such a limited light chain repertoire to pair with such a diverse heavy chain repertoire in any context. There certainly was not an expectation that a mouse constrained to produce only the limited light chain repertoire could be functionally successful at generating and selecting such a diverse set of heavy chains to produce functional antibodies with human variable domains.

(App. Br. 8–9).

We find this argument unpersuasive because the argument is not commensurate with the scope of claim 1. That is, claim 1 requires "a plurality of affinity-matured immunoglobulin heavy chains" with the "single rearranged human light chain variable region sequence" in the germline of

the mouse. While claim 1 may broadly encompass a large number of heavy chains, minimally the phrase "plurality" reasonably encompasses as few as two different heavy chains. The Specification explains that in "one embodiment, the fully human antigen-binding protein comprises a first heavy chain and a second heavy chain, wherein the first heavy chain and the second heavy chain comprise non-identical variable regions" (Spec. ¶ 56). Thus, even the Specification identifies an embodiment in with a "plurality" that comprises two different heavy chains.

Lonberg expressly teaches mice with a single light chain (FF 3, 6), and Lonberg reasonably suggests that while not all combinations of light and heavy chain will function (FF 6), Lonberg teaches:

> Rearranged light chain transgenes constructs that result in the highest level of human heavy/light chain complexes on the surface of the highest number of B cells, and do not adversely affect the immune cell compartment (as assayed by flow cytometric analysis with B and T cell subset specific antibodies), are selected for the generation of human monoclonal antibodies.

(FF 8). The teaching of human heavy/light chain complexes on B cells in the plural reasonably suggests that Lonberg expected at least two different heavy chains to interact with a particular rearranged light chain, as minimally required by claim 1.

Appellants contend

> the cited teachings would not have motivated one skilled in the art to achieve the claimed invention. Instead, they do nothing more than point out that rearranged immunoglobulin light chain variable region genes with somatically hypermutated sequences and germline sequences both exist at some point during B cell development, without providing any reasoned explanation as to why a skilled artisan would have been led specifically to

> engineer a mouse so that its germline contains only a single ***rearranged*** human light chain variable region sequence that comprises a ***human germline*** Vκ1-39 gene segment.

(App. Br. 10).

We find this argument unpersuasive because Lonberg specifically teaches: "Transgenic mice generated with the rearranged light chain constructs can be bred with heavy chain minilocus transgenics" (FF 5). Lonberg continues "mice, each containing different light chain constructs can be generated and tested" (FF 6). Thus, Lonberg expressly teaches the generation of transgenic mice with a single rearranged human kappa light chain (FF 4–6).

While Lonberg does not expressly state that the rearranged human kappa light chain are derived from a human germline kappa light chain variable region gene including the Vκ1-39 gene segment, de Wildt teaches that in using germline sequences, "[a]dditional diversity can be created by somatic hypermutation" (FF 16) and teaches the Vκ1-39 gene segment was a known equivalent human kappa light chain germline segment (FF 17). The Examiner reasons

> in order to ensure added diversity in the repertoire due to somatic mutation, it would have been *prima facie* obvious to the skilled artisan at the time of filing to select a germline rearranged human light chain variable region sequence rather than a rearranged sequence that has already undergone somatic hypermutation in response to a specific antigen. In regards to the selection of a human germline rearranged V-J variable region sequence IgKV1-39, de Wildt et al. teaches that Vk 02/12 (also known as Vk1-39) is one of the most common human V gene segments found in the human antibody repertoire and is capable of pairing with a large number of different heavy chain variable regions.

(Ans. 10). We agree with the Examiner that the ordinary artisan, interested in using Lonberg's transgenic mice with a single rearranged kappa light chain to obtain fully human antibodies (FF 6), would have used germline sequences including the Vκ1-39 gene segment prior to somatic hypermutation in order to maximize diversity of the finally obtained fully human antibodies as suggested by de Wildt (FF 16, *see* Ans. 10).

Appellants contend "none of the cited art individually discloses a mouse whose germline includes a light chain variable region gene that is both (1) rearranged and (2) includes a human germline gene segment" and "none of the cited references describe a claimed mouse that includes a single ***rearranged*** human light chain variable region sequence that comprises a ***human germline*** Vκ1-39 gene segment in its germline" (App. Br. 10–11).

We find this argument unpersuasive because the rejection is not an anticipation rejection solely relying upon one of Lonberg, Murphy, Mendez, or de Wildt alone, but rather is an obviousness rejection over the combined teachings of these four references, as well as "the background knowledge possessed by a person having ordinary skill in the art." *KSR*, 550 U.S. at 418. "It is well-established that a determination of obviousness based on teachings from multiple references does not require an actual, physical substitution of elements . . . Rather, the test for obviousness is what the combined teachings of the references would have suggested to those having ordinary skill in the art." *In re Mouttet*, 686 F.3d 1322, 1332–33 (Fed. Cir. 2012).

Appellants contend the "Examiner concludes that because Lonberg is silent about whether the amplified light chain sequences are somatically hypermutated, Lonberg provides motivation to use either somatically

mutated sequences or germline sequences. . . . However, silence cannot provide motivation" (App. Br. 11–12).

We find this argument unpersuasive because the Examiner does not, ultimately, rely upon Lonberg's silence for a reason to use germline sequences, but rather on de Wildt's teaching that through the use of germline sequences, "[a]dditional diversity can be created by somatic hypermutation" (FF 16). Because Lonberg also teaches a desire for diversity (FF 5), the ordinary artisan would have had reason to use de Wildt's germline sequences in Lonberg's rearranged kappa light chain to increase the level of diversity.

Appellants contend:

> The selection of a rearranged human immunoglobulin kappa light chain variable region gene is not a choice between two options - germline or somatically mutated. Rather, the options are potentially ***infinite***. As B cells develop, the sequences of the variable region genes are modified. As described above, combinatorial diversity and junctional diversity both contribute to variation in rearranged human immunoglobulin light chain variable region sequences within the primary antibody repertoire.

(App. Br. 13). Appellants reiterate the argument that "Lonberg's silence cannot reasonably be interpreted as a teaching to select any one specific sequence, for example, a single rearranged human light chain variable region sequence that comprises a human germline Vκ1-39 gene segment, from an infinite number of potential rearranged human immunoglobulin kappa light chain gene sequences" (*id.*).

We find these arguments unpersuasive because, as already discussed above, Lonberg teaches the use of "a reconstructed functionally rearranged kappa light chain transgene" (FF 4) and de Wildt states that additional

diversity added by somatic hypermutation is desirable (FF 16) and teaches that the Vκ1-39 gene segment is one of a set of known functional gene segments (FF 17). Thus, the Examiner is not solely arguing from Lonberg's silence, but rather from de Wildt's suggestion that "receptor editing operates in conjunction with somatic mutation to improve antibody affinities both by removing undesirable mutations and by creating further diversity" (FF 18). Therefore, the ordinary artisan interested in improving Lonberg's antibody affinity and improving Lonberg's diversity would have reasonably looked to de Wildt's somatic hypermutated germline sequences (*see, e.g.*, Ans. 17).

Appellants contend

> Lonberg discourages the selection of sequences from bone marrow B cells, teaching that the antibodies formed in the immature B cells (*i.e.*, the antibodies expressed from sequences that have not undergone somatic hypermutation) are of relatively ***low affinity***. Lonberg, ¶ [0216]. Lonberg's criticism, combined with its teaching to select sequences from cells which undergo somatic hypermutation, would have discouraged one of ordinary skill in the art from selecting germline sequences for inclusion in a rearranged human light chain variable region gene, and, therefore, teaches away from a claimed mouse that includes a single rearranged human light chain variable region sequence that comprises a human ***germline*** Vκ1-39 gene segment.

(App. Br. 14–15).

We find the teaching away argument unpersuasive because paragraph 216 of Lonberg includes no teaching away from somatic hypermutation or from germline cells. Instead, Lonberg teaches: "Because of the limited diversity generated by simple VJ and VDJ joining, the antibodies produced by the so-called primary response are of relatively low affinity" (FF 9). Indeed, Lonberg specifically teaches at paragraph 218 that "somatic

mutation during the secondary-response occurs throughout the V region including the three complementary determining regions" and that "[d]uring hypermutation, the rearranged DNA is mutated to give rise to new clones with altered Ig molecules. Those clones with higher affinities for the foreign antigen are selectively expanded" (FF 10).

Thus, Lonberg teaches that antibodies generated from the germline have some, if low affinity, which may be improved by somatic hypermutation (*see* FF 9–10). These teachings reinforce, rather than teach away, from the Examiner's finding that the ordinary artisan would have found it obvious to combine the use of germline sequences such as the Vκ1-39 taught by de Wildt with somatic hypermutation as suggested by both Lonberg and de Wildt (FF 4–6, 9, 10, 13, 16–18).

Appellants contend

> the Examiner has concluded that a skilled artisan would understand that certain light chain variable region gene segments are more likely to associate with heavy chain variable region gene segments. However, it must be noted that de Wildt's sample size of ***three*** makes it difficult to attribute significance to the pairings observed.

(App. Br. 16). Appellants contend "a skilled artisan reading de Wildt would not have been able to determine whether any heavy chain/light chain pairings occurred with an increased frequency in a single individual, or whether the heavy chain/light chain pairing occurred with an increased frequency in the collective three individuals" (App. Br. 17).

We find this argument unpersuasive because when applying the broadest reasonable interpretation none of the claims require the recited Vκ1-39 light chain to pair with more than two heavy chains. That is, claim 1 requires "a plurality of human V_H segments." However, neither the

Specification nor claim impose any particular requirements on the term "plurality" that require more than two different heavy chains.

This reading is consistent with the Examiner's finding that the artisan would have expected association of de Wildt's light chain sequences with multiple heavy chain sequences, satisfying the "plurality" requirement of claim 1. The Examiner specifically finds:

> the skilled artisan reading de Wildt et al. would have clearly understood that a demonstration that VK1-39 functionally associates with numerous different heavy chain sequences in IgG B cells inherently demonstrates that the rearranged germline VK1-39 variable region sequence expressed prior to somatic hypermutation was capable of functionally associating with numerous different heavy chain sequences.

(Ans. 16–17). Appellants, in the Reply Brief, do not directly dispute this finding, acknowledging that "de Wildt confirms, as was known in the art, that individual rearranged human germline immunoglobulin domain sequences can pair with heavy chains, that somatic hypermutation occurs, and that stable pairings can occur between a variety of heavy and light chains after somatic hypermutation" (Reply Br. 5–6).

In addition to arguing that de Wildt does not anticipate claim 1 and "cannot teach or suggest mice that express a population of antibodies as presently claimed" (App. Br. 18), Appellants also contend that "the data presented in Figure 1 do not necessarily reflect pairings that would occur in a presently claimed mouse comprising a single ***rearranged*** human light chain variable region sequence that comprises a ***human germline*** Vκ1-39 gene segment" (*id.*). Appellants further contend "the mere existence of rearranged germline immunoglobulin sequences *somewhere* in biology is far from establishing a *prima facie* case of obviousness over claims reciting a

mouse whose germline comprises *a single* ***rearranged*** human light chain variable region sequence that comprises a ***human germline*** Vκ1-39 gene segment" (App. Br. 20). Appellants contend "de Wildt provides *no guidance* to one skilled in the art to select *any particular germline* sequence" (Reply Br. 6).

We find these arguments unpersuasive because the person of ordinary skill, motivated by Lonberg to select human kappa light chain sequences (FF 1) for "mice generated with the rearranged light chain constructs" (FF 5), would have reasonably looked to other prior art references such as de Wildt that taught such human sequences, and selected functional human kappa light chain sequences such as the Vκ1-39 gene segment disclosed in de Wildt (FF 17). The claims "recite[] a combination of elements that were all known in the prior art, and all that was required to obtain that combination was to substitute one well-known . . . agent for another." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012).

Appellants do not provide evidence of any secondary consideration regarding the specific sequences that would have rendered their selection anything other than known equivalents. Therefore, such a combination is merely a "predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417.

Appellants contend

> none of the cited references, nor any combination thereof, teaches or suggests V_H1-2, V_H1-8, V_H1-18, V_H1-24, V_H2-5, V_H3-7, V_H3-9, V_H3-11, V_H3-13, V_H3-15, V_H3-20, V_H3-23, V_H3-30, V_H3-33, V_H3-43, V_H3-48, V_H4-31, V_H4-34, V_H4-59, or V_H6-1 (e.g., at least one of V_H2-5, V_H3-23, V_H3-30, and V_H4-59) in a mouse as presently claimed. de Wildt, either alone or in combination with other cited references, cannot teach or

> suggest the surprising result that that the V_H gene segments recited by the present claims are in fact utilized in antibodies produced in B cells of engineered mice comprising a single rearranged human light chain variable region sequence.

(App. Br. 21).

We find this argument unpersuasive because Appellants provide no evidence that this result is unexpected, whether by way of Declaration or citation to a statement in the Specification that this result is unexpected or otherwise surprising. "It is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements . . . [do] not suffice." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995)(citation and quotation marks omitted). This argument also fails to address the rejection in combination with Lonberg and Mendez, where Lonberg is relied upon to teach that "mice generated with the rearranged light chain constructs can be bred with heavy chain minilocus transgenics to produce a strain of mice that express a spectrum of fully human antibodies in which all of the diversity of the primary repertoire is contributed by the heavy chain" (FF 5) and Mendez teaches a number of heavy chain segments including V_H2-5, V_H3-23, V_H3-30, and V_H4-59 (FF 14). *Merck*, 800 F.2d at 1097.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that the prior art suggests a mouse with a "single rearranged human light chain variable region sequence comprises a human germline Vκ1-39 gene segment" and "one of V_H2-5, V_H3-23, V_H3-30, and V_H4-59" as required by claim 1.

B. Obviousness-type Double Patenting

We summarily affirm the obviousness-type double patenting rejections because Appellants do not dispute the merits of these rejections (*see* App. Br. 24). *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.]")

SUMMARY

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Lonberg, Murphy, Mendez, and de Wildt. Claims 2–6 and 9–23 fall with claim 1.

We affirm the rejections of claims 1–6 and 9–23 on the ground of nonstatutory double patenting as being unpatentable over: Claims 1–10, 12–13, and 15–34 of copending Application No. 13/092, 156; Claims 1–8, 10–17, and 19–21 of copending Application No. 13/022,759; Claims 1, 2, and 4–18 of copending application 13/412,936; and Claims 14–27 of copending Application 13/798,310.

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