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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LEE M. **KAPLAN**,
ALICE P. LIOU, PETER J. TURNBAUGH, and JASON L. HARRIS,

Junior Party
(Patents 10,149,867; 10,149,870; and 10,729,732;
and Application 16/159,021),

v.

PATRICE **CANI**,
AMANDINE EVERARD, CLARA BELZER, and WILLEM DE VOS,

Senior Party
(Application 14/443,829).

Patent Interference No. 106,130 (DK)

Decision on Priority
37 C.F.R. § 41.125(a)

Before DEBORAH KATZ, RACHEL H. TOWNSEND and
DAVID COTTA, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

I. Introduction

Kaplan has been accorded benefit of the filing date, February 28, 2013, of its prior U.S. Application No. 13/780,284. (*See* Third Redeclaration, Paper 351, 3.) Cani has been accorded benefit of the filing date, November 19, 2012, of its prior International Application No. PCT/EP2012/073011. (*See id.*) "[P]riority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice." *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998). Because Cani has not filed a priority motion, relying instead on its accorded benefit date, if Kaplan can show that its inventors reduced an embodiment of the count to practice before November 19, 2012, or conceived of an embodiment and diligently worked towards a reduction to practice before that date, it will prevail on priority. *See* 37 C.F.R. § 41.121(b) ("The party filing the motion has the burden of proof to establish that it is entitled to the requested relief.").

As explained in detail below, we determine that Kaplan has failed to present sufficient evidence to support its arguments for a reduction to practice or conception earlier than Cani's accorded priority date. Accordingly, we are not persuaded that Kaplan should be granted priority of invention for the subject matter of the count.

II. Analysis

When evaluating the testimony of an inventor, we look to corroborative,

independent evidence to safeguard against inventors who might otherwise "be tempted to remember facts favorable to their case." *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341, 1346 (Fed. Cir. 2017). Kaplan bears the burden of providing a showing, supported by appropriate evidence, of the motions it asserts. *See* 37 C.F.R. § 41.208(b) and § 41.121(b). We evaluate the parties' arguments and evidence of dates of conception and reduction to practice to determine whether the preponderance of the evidence supports Kaplan's arguments. *See* 37 C.F.R. § 41.207(a)(2).

"A conception must encompass all limitations of the claimed invention." *Singh v. Brake*, 317 F.3d 1334, 1340 (Fed. Cir. 2003); *see Taurus IP, LLC v. DaimlerChrysler Corp.*, 726 F.3d 1306, 1323 (Fed. Cir. 2013); *Slip Track Sys., Inc. v. Metal-Lite, Inc.*, 304 F.3d 1256, 1263 (Fed. Cir. 2002); *Brown v. Barbacid*, 276 F.3d 1327, 1336 (Fed. Cir. 2002). Conception requires more than "a general goal or research plan," it requires a "definite and permanent," "specific, settled idea," namely, the idea defined by the claim at issue. *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994); *see REG Synthetic Fuels, LLC v. Neste Oil Oyj*, 841 F.3d 954, 962 (Fed. Cir. 2016). Conception requires a "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986); *see also Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991) ("Conception requires both the idea of the invention's structure and possession of an operative method of making it."). "[C]onception requires that the inventor appreciate that which he has invented. . . . and that he understood his

creation to have the features that comprise the inventive subject matter at bar." *See Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1063–64 (Fed. Cir. 2005).

A. Count Interpretation

Count 1 of the interference includes four alternatives, each including claim 1 of Cani involved application 14/443,829 and a different claim of an involved Kaplan patent or application. (*See* Declaration, Paper 1, 5:2–6:6; Second Redeclaration, Paper 23, 2:4–7.) Kaplan argues its priority case based on the Kaplan portion of the 1(a) alternative of the count. (*See* Kaplan Motion 3, Paper 362, 3:2–9.) Alternative 1(a) of Count 1 includes claim 1 of Kaplan involved Patent No. 10,149,870, which is identical to claim 1 of Cani involved application 14/443,829, and recites:

> A method for treating a metabolic disorder in a subject in need thereof, the method comprising orally administering a composition comprising a therapeutically effective amount of bacteria comprising substantially purified *Akkermansia* to the subject wherein the substantially purified *Akkermansia* comprises at least 50% of a strain of *Akkermansia*.

(Cani Clean Copy of Claims, Paper 13, A-1; Kaplan Clean Copy of Claims, Paper 8, 2:2–5.)

"Interference counts are given the broadest reasonable interpretation possible, and resort to the specification is necessary only when there are ambiguities inherent in the claim language or obvious from arguments of counsel." *DeGeorge v. Bernier*, 768 F.2d 1318, 1321–22 (Fed. Cir. 1985); *see Davis v. Loesch*, 998 F.2d 963, 968 (Fed. Cir. 1993). The 1(a) alternative of the count

recites a "therapeutically effective amount of bacteria," "substantially purified *Akkermansia*," and "at least 50% of a strain of *Akkermansia*." The parties disagree about how much *Akkermansia* is required in light of these terms. Kaplan argues that the recited orally administered composition does not require a minimum amount or concentration of *Akkermansia* and can encompass even non-effective amounts of *Akkermansia*, whereas Cani argues that the composition comprises at least 50% *Akkermansia*. After reviewing the parties' arguments and evidence, as discussed in detail below, we are persuaded that the count requires at least a therapeutically effective amount of *Akkermansia* in the composition as a whole. As explained below, we are not persuaded that Kaplan's very broad interpretation is reasonable because it does not consider the arguments and statements made during prosecution that resulted in allowable subject matter.

1. "*Therapeutically effective amount of bacteria"*

The 1(a) alternative of the count requires that the orally administered composition comprises a "therapeutically effective amount of bacteria" and this amount "compris[es] substantially purified *Akkermansia*." (Cani Clean Copy of Claims, Paper 13, A-1; Kaplan Clean Copy of Claims, Paper 8, 2:2–5.) We first determine whether the 1(a) alternative of the count is limited by a therapeutically effective amount of *Akkermansia* in the orally administered composition.

As Cani argues, during prosecution of application 15/698,965 ("the '965 appl."), which became the '870 patent and the claim that is the Kaplan portion of the 1(a) alternative of the count, Kaplan distinguished the then pending claims over the cited prior art by noting that the claims are directed to the selection of *Akkermansia* over other bacteria to treat a metabolic disease. (*See* Cani Opp. 3,

Paper 371, 10:30–11:15.) Claim 28, the only pending independent claim, and claim 48 of application 15/698,965 ("the '965 appl.") were presented as:

> 28. (Currently Amended) A method for treating a metabolic disorder in a subject in need thereof, the method comprising orally administering a composition comprising a therapeutically effective amount of bacteria comprising substantially purified *Akkermansia* to the subject.
>
> 48. (New) The method according to claim 28, wherein if the bacteria comprise a mixture of bacterial strains, then at least 50% of the bacterial strains in the composition are *Akkermansia.*

(Amendment submitted August 24, 2018 in '965 appl., Ex. 2027, 2–3 (underlining in original to indicate language added by amendment).) Claim 28 included the same limitation as the 1(a) alternative of the count, wherein the "composition compris[es] a therapeutically effective amount of bacteria comprising substantially purified *Akkermansia*."

To overcome the prior art cited by the Examiner, Kaplan argued:

> Sadowsky relates to extracts and preparations of human feces, and thus describes a composition that would contain a diverse range of many species and strains of different bacteria. For example, claim 23 of Sadowsky recites a composition that comprises "at least 4 different phyla of bacteria, wherein the phyla comprise a Bacteroidetes, a Firmicutes, a Proteobacteria, a Tenericutes phyla, or a combination thereof," (referring to claim 22 of Sadowsky) and "further comprises at least 5, 6, 7, 8, 9 or 10 different classes of bacteria chosen from Actinobacteria, Bacteroidia, Bacilli, Clostridia, Erysipelotrichi, Alphaproteobacteria, Betaproteobacteria, Gammaproteobacteria, Mollicutes and Verrumicrobiae." (Sadowsky, claim 23) Sadowsky does not contemplate selecting a *particular* genus for use with the composition. In stark contrast, the presently amended claims are

> directed to orally administering a therapeutically effective amount of substantially purified *Akkermansia*.

(Amendment submitted August 24, 2018 in '965 appl., Ex. 2027, 6–7.) Cani argues that this statement indicates Kaplan considered its claims to be patentable because the *Akkermansia* itself is therapeutically effective. (*See* Cani Opp. 3, Paper 371, 10:30–33.)

In addition, Cani cites a declaration by inventor Kaplan that was submitted during prosecution of the '965 application. (*See* Cani Opp. 3, Paper 371, 11:6–15.) In the Declaration, Dr. Kaplan distinguished the invention over another prior art reference, stating:

> Derrien's failure to suggest the selection of *A. muciniphila* over a single alternative should be considered in the context of the many thousands of other bacteria that were known and available for selection. There is insufficient basis in Derrien (i) to reasonably believe that *A. muciniphila* could be sufficient to treat a metabolic disease; or (ii) select *A. muciniphila* over any other bacterium.

(Declaration of Dr. Lee Kaplan Under 37 C.F.R. § 1.132, submitted August 24, 2018 in '965 appl., Ex. 2028, ¶ 18.) Dr. Kaplan asserted that the claims were patentable over prior art that does not teach selecting *Akkermansia* (specifically, the species *Akkermansia muciniphila* or *A. muciniphila*) over any other bacteria as a treatment for metabolic disease and does not teach *A. muciniphila* would be a sufficient treatment. Dr. Kaplan characterized the invention as providing a sufficient treatment for a metabolic disease, wherein *A. muciniphila* is selected over other bacteria. We agree with Cani's characterization of Kaplan's position during prosecution that the claims were patentable because of the selection of

Akkermansia to treat a metabolic disease and because *Akkermansia* itself was therapeutically effective. (*See* Cani Opp. 3, Paper 371, 10:16–22.)

According to Kaplan, though, the prosecution history fails to show a clear disavowal of the scope of the 1(a) alternative of the count. (*See* Kaplan Reply 3, Paper 376, 4:17–5:5.) Kaplan argues that the statements highlighted by Cani refer to characterizations of prior art or claims that were not allowed and that are materially different from the count, such as claim 48. (*See id.*)

We are not persuaded by Kaplan's arguments because we find that the statements made during prosecution to be a clear characterization of how the claimed invention is different from and patentable over the prior art and, thus, what the scope of the allowable subject matter is. Kaplan clearly defined the scope of the claims as requiring the selection of a therapeutically effective amount of *Akkermansia* bacteria over other bacteria for the recited composition. (*See* Amendment submitted August 24, 2018 in '965 appl., Ex. 2027, 6–7; *see* Declaration of Dr. Lee Kaplan Under 37 C.F.R. § 1.132, submitted August 24, 2018 in '965 appl., Ex. 2028, ¶ 18.).) Kaplan's statements to obtain allowance of the claim that became part of the count clearly disavow a scope that encompasses a composition having an amount of *Akkermansia* but no therapeutic effect from it, when present by itself or when present in a mixture of bacteria. Kaplan's statements indicate that the composition must include an amount of *Akkermansia* sufficient to be therapeutically effective.

Accordingly, we interpret the 1(a) alternative of the count to be limited to orally administering a composition, wherein the amount of *Akkermansia* bacteria is therapeutically effective.

2. "Substantially purified Akkermansia"

Kaplan argues that the term "substantially purified *Akkermansia*" in the 1(a) alternative of the count is the equivalent of the *Akkermansia* being "substantially enriched" in the orally administered composition. (*See* Kaplan Motion 3, Paper 362, 3:19–21.) Kaplan cites the specification of its involved patent for the interpretation of the term "substantially purified." (*See id.* (quoting '870 patent, Ex. 1001, 17:18–22.) The '870 patent[1] states:

> The microbiota can also be substantially purified. The term "substantially purified" as used herein refers to a bacterial strain or a mixture of more than one bacterial strains (e.g., Bacteroidetes, Firmicutes, Proteobacteria, or Verrucomicrobia) that are substantially enriched in a sample. The sample can be substantially purified or enriched for the bacterial strain or mixture of strains of interest such that the sample is at least about 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99% or greater of the desired bacterial strain(s) or less than about 40%, 30%, 20%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or less of the undesirable or other bacterial strains present.

(Ex. 1001, 17:18–29.) Kaplan argues that this portion of the '870 patent specification defines "substantially purified" as a bacterial strain or a mixture of more than one bacterial strain that is "substantially enriched." (*See* Kaplan Motion 3, Paper 362, 3:18–22; *see* Kaplan Reply 3, Paper 376, 1:14–17.) Kaplan

[1] The same language is also present at paragraph 80 in provisional application 61/604,824, to which the '870 patent cites for priority. (*See* Ex. 1010, ¶ 80.)

emphasizes the equivalence of "substantially purified" with "substantially enriched," without further defining or limiting the term "substantially enriched."

In support of its argument, Kaplan relies on the testimony of its witness, Dr. Goodman,[2] that based on the first sentence of the quoted portion of the '870 patent, "'a composition comprising a therapeutically effective amount of bacteria comprising substantially purified *Akkermansia*' [means] that the composition comprising therapeutically effective bacteria must include substantially enriched *Akkermansia,* and may also include bacteria other than *Akkermansia* or other components." (Third Goodman Decl., Ex. 1628, ¶ 18.) We agree with Kaplan that in light of the phrases "substantially purified" and "comprising" in the 1(a) alternative of the count and Dr. Goodman's testimony, the count recites a composition that can include bacteria other than *Akkermansia*. (*See* Kaplan Motion 3, Paper 362, 3:22–24.) Cani does not argue to the contrary.

But Kaplan's asserted interpretation provides no limits on the amount or concentration of *Akkermansia* in the recited composition necessary to qualify as "substantially enriched." In regard to the percentage ranges of the desirable (50% . . . 99% or greater) and undesirable (40% . . . 1% or less) bacteria strains provided in the specification, Kaplan argues that the permissive language "can be" is used rather than the restrictive language "must." (*See* Kaplan Reply 3, Paper 376, 1:22–2:3 (referring to the language of Ex. '870 patent, Ex. 1001, 17:18–29).) Thus, according to Kaplan, the language in the specification of the '870 patent referring

[2] We reviewed the credentials of Dr. Goodman and determined that he is qualified to testify about the subject matter of Count 1in the Decision on Motions. (*See* Paper 350, 3–4.)

to percentages of "substantially purified" bacteria in a sample are not limiting on the 1(a) alternative of the count.

Furthermore, Kaplan cites Dr. Goodman's testimony that even though he previously testified in this proceeding that "[a] POSA would have understood the term 'substantially purified' in [Kaplan's provisional application] to *include* embodiments with greater than 99% purity, that is, with just trace contamination," his testimony did not mean that "substantially purified" embodiments *must* be embodiments with greater than 99% purity. (Third Goodman Decl., Ex. 1628, ¶ 20 (quoting First Goodman Decl., Ex.1501, ¶ 163); *see* Kaplan Motion 3, Paper 376, 3:22.) According to Dr. Goodman, "while 'substantially purified' may encompass embodiments with greater than 99% purity, it also encompasses embodiments that include substantially enriched *Akkermansia,* but may also include bacteria other than *Akkermansia* or other components." (Third Goodman Decl., Ex. 1628, ¶ 20.)

Kaplan further supports its argument that the term "substantially purified *Akkermansia*" encompasses almost any amount or concentration of *Akkermansia* in the orally administered composition by citing the testimony of Dr. Hill,[3] Cani's witness, that "[i]ncreasing the relative abundance of a bacterium from 0.0001% to 0.001% would represent substantial enrichment . . . ."[4] (Third Hill Decl., Ex. 2324,

[3] We reviewed the credentials of Dr. Hill and determined that he is qualified to qualified to testify about the subject matter of Count 1in the Decision on Motions. (*See* Paper 350, 2–3.)

[4] Dr. Hill also testifies further if you increase bacterium from 0.0001% to 0.001% "you could not consider it to be substantially purified." (Third Hill Decl., Ex. 2324, ¶ 41.)

¶ 41; *see* Kaplan Reply 3, Paper 376, 1:19–21.) According to Kaplan, a concentration of *Akkermansia* that had increased to, but was still as low as 0.001% within a mixture of other bacteria would be within the scope of the 1(a) alternative of the count.

Kaplan argues further that Dr. Hill testified on cross-examination that "substantially purified" is defined in the '870 patent as "a bacterial strain or a mixture of more than one bacterial strains . . . that are ***substantially enriched*** in a sample." (*See* Kaplan Reply 3, Paper 376, 1:15–18 (citing Hill Depo., Ex. 1637, 228:22–231:2).) We note, though, that Kaplan does not cite to testimony in which Dr. Hill agreed that the term "substantially purified" as used in the count could be considered by one of ordinary skill in the art to have the same scope as "substantially enriched" and encompass almost any amount or concentration of *Akkermansia*.

Kaplan's argument for the lack of a limit on the amount or concentration of *Akkermansia* in the orally administered composition in the count is based almost entirely on the language of the '870 patent specification equating the term "substantially purified" with "substantially enriched." Kaplan argues that "Kaplan's lexicography should control," but we are not persuaded that the '870 patent was drafted to clearly define "substantially purified" as simply encompassing any increase in the concentration of *Akkermansia* in a mixture of bacteria. (*See* Kaplan Reply 3, Paper 376, 1:14.) *See CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002) ("Generally speaking, we indulge a "heavy presumption" that a claim term carries its ordinary and customary meaning. . . . First, the claim term will not receive its ordinary meaning if the

patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term in either the specification or prosecution history."). We are not persuaded that, when read in its entirety, and considering the prosecution history of the claim that became the 1(a) alternative of the count, the specification contemplates encompassing simply any increased concentration in the terms "substantially purified" and "substantially enriched." We are not persuaded that the inclusion of exemplary concentrations in the specification, particularly the exemplary ranges of "at least about 50% . . . or greater" of the desired bacterial strain(s) or less than or about 40% . . . or less of the undesirable or other bacterial strains present" have no effect on the broadest reasonable interpretation of the count. ('870 patent, Ex. 1001, 17:18–29.)

Kaplan's argument focuses on the phrase "substantially purified," without giving any separate effect to the phrase "therapeutically effective amount." For example, Kaplan urges that "the therapeutically effective amount of bacteria comprises substantially purified *Akkermansia*," and then proceeds only to define "substantially purified" as being the same thing as substantially enriched. (Kaplan Motion 3, Paper 362, 3:18–19.) Similarly, Dr. Goodman testifies that a "therapeutically effective" amount of bacteria that comprises substantially enriched *Akkermansia* in the 1(a) alternative of the count "does not require that the substantially enriched *Akkermansia* be the sole therapeutically effective strain of bacteria, or even that the *Akkermansia* itself be therapeutically effective." (Third Goodman Decl., Ex. 1628, ¶ 21.) Because, as discussed above, Kaplan's statements to obtain allowance of the claim that became part of the count indicated a requirement that the orally administered composition include an amount of

Akkermansia sufficient to be therapeutically effective, we are not persuaded that the simple equivalence between the terms "substantially purified" and "substantially enriched" in the specification is the only factor to consider in the interpretation of the 1(a) alternative of the count. We do not agree that Kaplan's extremely broad interpretation, encompassing a composition with potentially any amount of *Akkermansia* (including amounts so small as to have no therapeutic effect), and any amount of other bacteria, is reasonable in light of the totality of the record Kaplan created regarding the invention recited in the count.

Our determination is supported by statements and arguments Kaplan has made earlier this proceeding. Specifically, Cani highlights Kaplan's position in Kaplan Motion 2 of this proceeding, seeking benefit of an earlier filing date as to the count. (*See* Cani Opp. 3, Paper 371, 6:4–7:22.) In that motion, Kaplan argued that "[t]he term 'substantially purified' is defined to include purity with only trace contamination," citing the language in the specification. (Kaplan Motion 2, Paper 84, 6:9–10 (citing provisional appl. '824, Ex. 1010, ¶ 80); *see* Cani Opp. 3, Paper 371, 6:11–25.) Kaplan argued further in its Motion 2:

> Similarly, Provisional '824 supports a substantially pure strain, where substantially pure expressly includes at least 50% to greater than 99% purity (emphasis added):
>
> > The microbiota can also be **substantially purified**. The term "substantially purified" as used herein refers to a bacterial strain or a mixture of more than one bacterial strains (e.g., ... *Verrucomicrobia*) that are substantially enriched in a sample. The sample can be substantially purified or enriched for the bacterial strain or mixture of strains of interest such that the sample is **at least about**

> **50%**, ... **99% or greater** of the desired bacterial strain(s) or less than about 40%, ... 1% or less of the undesirable or other bacterial strains present. In an exemplary embodiment, a composition includes substantially purified *Verrucomicrobia*.

EX1010, ¶80; MF17; EX1501, ¶173.

(Kaplan Motion 2, Paper 84, 9:6–16; *see* Cani Opp. 3, Paper 371, 7:1–18.) Kaplan highlighted the terms "substantially pure" and "at least about 50%, … 99% or greater," but did not highlight or mention the term "substantially enriched," in its previous argument. (*Id.*) Kaplan's focus during the first phase of this proceeding was on a narrower interpretation of the term "substantially purified."

Kaplan argues that its previous argument was that the scope of "substantially purified" *includes* purity with only trace contamination, but is not *limited* to this high level of purity. (*See* Kaplan Reply 3, Paper 376, 2:14–19.) Kaplan also argues that its previous argument, and the corresponding decisions of the Board, were relevant to the language of the 1(c) alternative of the count, not the 1(a) alternative, on which Kaplan now bases its priority case. (*See id.* at 2:12–14.)

Although Kaplan is not wrong that a broad interpretation of "substantially purified" would encompass higher levels of purity as well as lower levels of purity, we are not persuaded that Kaplan should prevail on a very broad interpretation of the same phrase in its priority case when its previous arguments focused on a narrow interpretation of the same phrase. (*See* Kaplan Reply 3, Paper 376, 2:14–19.) We are also not persuaded that the phrase "substantially purified" should be interpreted differently in different alternatives of the count. Kaplan provides no

substantive reason why this phrase should be different in alternative 1(c) than in alternative 1(a).

Kaplan argues that "the Federal Circuit has held claim construction is a 'rolling' process, since it is a conclusion of law that may evolve as the record and disputes develop," but Kaplan cite to support holding that a party may change its interpretation of the same phrase during different phases of a proceeding. (*See* Kaplan Reply 3, Paper 376, 2:20–23. Rather, in *Jack Guttman, Inc. v. Kopykake Enters., Inc.*, 302 F.3d 1352, 1361 (Fed. Cir. 2002), the case Kaplan cites, the Federal Circuit explained that "*[d]istrict courts* may engage in a rolling claim construction, in which *the court* revisits and alters its interpretation of the claim terms as its understanding of the technology evolves." (Emphasis added.) Accordingly, Kaplan cannot explain away its inconsistent claim construction positions on the basis that claim construction is a "rolling" process, particularly where it offers no persuasive reasoning to support its change in positions.

After reviewing the totality of the record regarding Kaplan's interpretation of the term "substantially purified *Akkermansia*" in the 1(a) alternative of the count, we are not persuaded that the count as a whole is reasonably interpreted to encompass an orally administered composition with any concentration or amount of *Akkermanisa* that is "substantially enriched" if it does not also include an amount of *Akkermansia* sufficient to be therapeutically effective.

3. "Comprises at least 50% of a strain of Akkermansia"

The parties disagree about the effect of the last phrase in the 1(a) alternative of the count: "wherein the substantially purified *Akkermansia* comprises at least 50% of a strain of *Akkermansia*." According to Kaplan, only the portion of the

composition comprising "substantially purified *Akkermansia*" comprises at least 50% of a strain of *Akkermansia*, not the entire composition of bacteria. (*See* Kaplan Motion 3, Paper 362, 3:24–25.) Put another way, Kaplan contends that if the composition comprises bacteria that are not *Akkermansia,* those bacteria are not considered when determining whether the "50% of a strain of *Akkermansia*" claim requirement is met. In contrast, Cani argues that the 1(a) alternative of the count is properly interpreted to require a composition in which *Akkermansia* is present in a therapeutically effective amount comprising at least 50% of the bacteria in the composition. (Cani Opp. 3, Paper 371, 12:15–23 (citing Third Hill Decl., Ex. 2324, ¶ 42).)

Cani argues that Kaplan's interpretation of the phrase - wherein the *Akkermansia* in the composition comprises at least 50% of a strain of *Akkermansia* – makes the 50% limitation superfluous because "[i]f there is only one *Akkermansia*, i.e., *Akkermansia muciniphila* [as Kaplan reportedly asserts], then it makes no sense to require that there be 50 percent of that same strain." (Cani Opp. 3, Paper 371, 8:7–9.) We are not persuaded by Cani's argument because Cani's witness, Dr. Hill, testifies it was known that *Akkermansia* would have various strains. (*See* Hill Depo., Ex. 1637, 95:22–97:12 ("Q. Okay. Like, for example, Akkermansia muciniphila could have, itself, various strains; right? A. Not only could, but does. . . . Q. Okay. But you would agree with me that persons of skill in the art in the late 2011/early 2012 time frame at least were aware that there were multiple strains of *Akkermansia muciniphila*; right? A. I mean, that would have been an absolutely safe assumption, yes."); *see* Kaplan Reply 3, Paper 376, 3:19–4:4.) Accordingly, Kaplan's proposed interpretation of "at least 50% of a strain of

Akkermansia" does not render the phrase meaningless because multiple strains of *Akkermansia* were known in the art. Thus, we are not persuaded that the amount of *Akkermansia* in the overall composition recited in the Kaplan portion of the 1(a) alternative of the count is limited by the phrase "at least 50% of a strain of *Akkermansia*."

We are also not persuaded by Cani's argument that the Reasons for Allowance limits the count to a composition that is at least 50% *Akkermansia*. (*See* Cani Opp. 3, Paper 371, 11:27–12:11.) In the Reasons for Allowance the examiner stated: "The invention is directed to a method for treating a metabolic disorder in a subject comprising orally administering to the subject a composition comprising a therapeutically effective amount of bacteria having at least 50% of a strain of *Akkermansia.*" (Notice of Allowance in appl. 15/698,965, Ex. 2030, 7–8; *see* Cani Opp. 3, Paper 371, 11:27–12:11.) But, as Kaplan argues, where there is not a clear and unmistakable acquiescence to an examiner's characterization, such examiner's statements do not necessarily control. (*See* Kaplan Reply 3, Paper 376, 5:16–6:3 (citing *Salazar v. Procter & Gamble Co*., 414 F.3d 1342, 1345 (Fed. Cir. 2005) (This court has recognized that an Examiner's Statement of Reasons for Allowance "will not necessarily limit a claim." (citation omitted)).) In addition, Kaplan generically disavowed the examiner's reasons for allowance. (*See* Ex. 2322 ("Entry of the [the Examiner's Statement of Reasons for Allowance] into the record should not be construed as any agreement with or acquiescence in the reasoning stated by the Examiner.").) Thus, the examiner's statement does not limit the scope of Kaplan's portion of the count to at least 50% of a strain of *Akkermansia*.

Whereas Cani's arguments are unpersuasive, we are persuaded by Kaplan's arguments that the phrase "wherein the substantially purified *Akkermansia* comprises at least 50% of a strain of *Akkermansia*" does not limit the entire composition recited in the Kaplan portion of the 1(a) alternative of the count. (*See* Kaplan Reply 3, Paper 376, 3:8–11; *see* Third Goodman Decl., Ex. 1628, ¶ 19 ("The plain language of Count 1(a) provides that the "substantially purified *Akkermansia* comprises at least 50% of a strain of *Akkermansia.*" It does not state, as Cani's potential argument would require, that the ***composition*** is at least 50% of a strain of *Akkermansia*.").) Nevertheless, as discussed above, Kaplan's interpretation of the 1(a) alternative of the count as being so broad as to encompass *any* concentration of *Akkermansia* in a mixture of more than one type of bacteria is unreasonable. Instead, we are persuaded that the 1(a) alternative of the count is properly interpreted as limited to a composition with at least a therapeutically effective amount of *Akkermansia* within a mixture of more than one type of bacteria.

4. Conclusion

Accordingly, based on the totality of the record, in order to show priority Kaplan must cite sufficient evidence that the inventors reduced to practice and/or conceived of a method of orally administering a composition to treat a metabolic disorder, wherein the amount of *Akkermansia* bacteria in the composition administered is therapeutically effective**.** The *Akkermansia* recited in the 1(a) alternative of the count is also limited to comprising at least 50% of a strain of *Akkermansia*. (*See* Kaplan Motion 3, Paper 362, 3:24–25.)

B. *Conception*

Kaplan cites the results of two studies performed by the inventors about the contribution of the gut microbiota to energy and glucose homeostasis as evidence of conception and reduction to practice. (*See* Kaplan Motion 3, Paper 362, 5:19–23:14.) Specifically, Kaplan argues that Dr. Kaplan developed a mouse model of Roux-en-Y gastric bypass ("RYGB") surgery to study changes in the mouse-gut microbiome after surgery and to determine whether any benefits could be transferred without surgery. (*See id.* at 4:13–5:5 (citing, *inter alia*, Kaplan Decl., Ex. 1624, ¶ 43; Detailed Protocol, Ex. 1581).) Kaplan describes the study as having two phases.

In the first phase, groups of mice were freely fed a high-fat diet ("HFD") and underwent either RYGB surgery or a control ("sham") surgery. (*See id.* at 6:6–20.) These groups of mice were compared to each other and to a control group of mice that had undergone sham surgery, but were on a restricted diet (the weight-matched mice ("WMS") group). (*See id.*) In the second phase of the study, the cecal contents of groups of mice from the first phase (RYGB, Sham, and WMS) were administered to germ-free mice to determine the effect of RYGB-altered microbiota on body weight gain and glucose intolerance. (*See id.* at 6:21–7:7.)

Kaplan argues that the results of the first phase showed that the mice in the RYGB surgery group exhibited a trend towards decreased body weight compared to controls. (*See id.* at 8:6–11.) Kaplan argues further that results from the second phase showed that mice receiving transfer of cecal contents from RYGB mice also exhibited a trend towards decreased body weight and adiposity compared to germ-free mice that had not received any transfer. (*See id.* at 8:6–11.) Kaplan argues

that the inventors concluded from these results that RYGB microbiota might drive decreased body weight and adiposity. (*See* Kaplan Motion 3, Paper 362, 8:11–13 (citing, Kaplan Decl., Ex. 1624, ¶ 53; Liou Decl., Ex. 1626, ¶ 36; Turnbaugh Decl., Ex. 1625, ¶ 34).) Kaplan argues further that an update to this first phase study supported the earlier results, wherein mice receiving a transfer of RYGB cecal contents had statistically-significant lower body weights and a trend towards decreased adiposity compared to germ-free control mice that had not received a transfer. (*See* Kaplan Motion 3, Paper 362, 8:14–16.)

Kaplan cites a presentation by Dr. Liou, dated July 6, 2011, to corroborate the inventors' testimony about their conclusions that cecal contents from RYGB mice decrease body weight and adiposity in mice. (*See id.* at 7:21–8:6.) The presentation states: "If the following observations are consistent and repeatable, then RYGB microbiota may be driving a signaling mechanism responsible for decreased body weights [and] decreased adiposity." (Ex. 1586, 26.) Kaplan does not direct us to discussion or acknowledgement of a therapeutic effect of *Akkermansia* in the July 6, 2011 presentation. Nor does Dr. Liou's or Dr. Kaplan's testimony about the presentation discuss or acknowledge a therapeutic effect of *Akkermansia* or orally administering a therapeutically sufficient amount of *Akkermansia* to treat a metabolic disorder. (*See* Liou Decl., Ex. 1626, ¶¶ 34–36; *see* Kaplan Decl., Ex. 1624, ¶¶ 51–53.)

Kaplan argues further that on July 27, 2011, Dr. Liou provided another update on the studies, which Kaplan asserts allowed the inventors to "experimentally confirm[] that oral administration of RYGB microbiota could be used to treat metabolic disorders." (Kaplan Motion 3, Paper 362, 8:17–9:5 (citing

Kaplan Decl., Ex. 1624, ¶ 55; Liou Decl., Ex. 1626, ¶ 38).) The presentation states: "If our results are real and repeatable, this implies that microbial communities from RYGB mice reverse the normal phenomenon from happening!!" (July 27, 2011 Presentation, Ex. 1587, 10, 13.) The presentation also states: "If the following observations are consistent and repeatable, then RYGB microbiota may be driving a signaling mechanism responsible for decreased body weights and decreased adiposity." (*Id.* at 13.) Kaplan does not direct us to discussion or acknowledgement of a therapeutic effect of *Akkermansia* or of orally administering a therapeutically sufficient amount of *Akkermansia* to treat a metabolic disorder in the July 27, 2011 presentation or in Dr. Liou's testimony or Dr. Kaplan's testimony about this presentation or an earlier presentation dated July 6, 2011. (*See* Liou Decl., Ex. 1626, ¶¶ 37–38; *see* Kaplan Decl., Ex. 1624, ¶¶ 54–55.)

Kaplan argues that on August 29, 2011, Dr. Turnbaugh performed sequencing analysis that reportedly identified *Akkermansia* as a microbe that could serve as an oral therapeutic for the treatment of metabolic disorders. (*See* Kaplan Motion 3, Paper 362, 9:8–19.) According to Kaplan, Dr. Turnbaugh's sequencing showed that "post-surgery mice exhibited a significant increase in the abundance of *Akkermansia* in the gut, with the greatest fold increase in RYGB mice." (Kaplan Motion 3, Paper 362, 9:10–11.) Kaplan cites to Exhibit 1588, which is described only as "P. Turnbaugh RYGB 16S Data, Notes (Aug. 29, 2011 to Nov. 26, 2011" and includes the entry: "-another curious finding is that that mice have high levels of Verrucos (A. muciniphila)." (Ex. 1588, 1.) Dr. Turnbaugh testifies that his sequencing analysis of August 29 "identified *Akkermansia* as a microbe

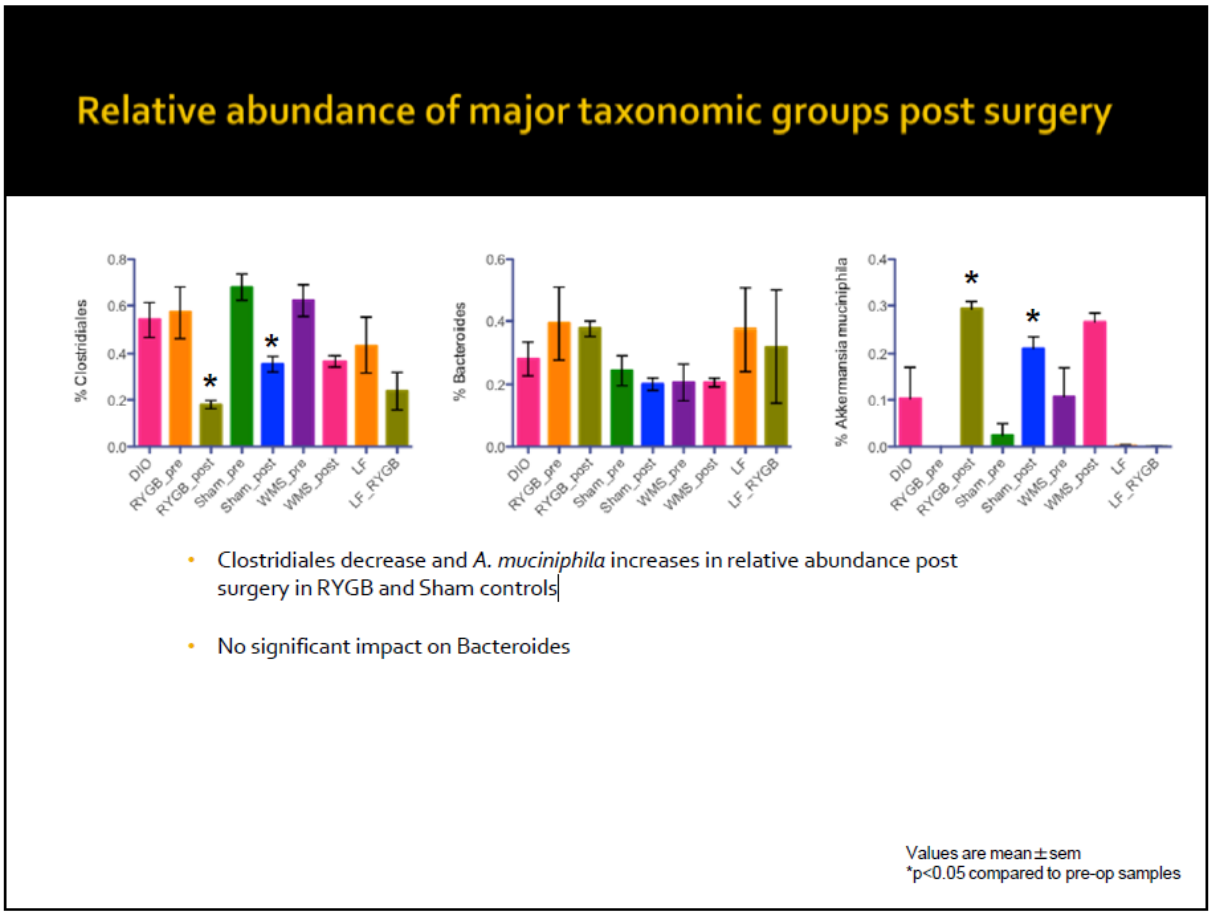
that may be used as an oral therapeutic treatment of metabolic diseases," citing Exhibit 1588. (Turnbaugh Decl., Ex. 1625, ¶¶ 36–37.)

Although Exhibit 1588 mentions an increase in the amount of *Akkermansia* in RYGB mice, it does not refer to an oral therapeutic treatment for any disease. Exhibit 1588 fails to corroborate Dr. Turnbaugh's testimony that *Akkermansia* was identified as an oral therapeutic treatment because Exhibit 1588 does not indicate an acknowledgement of a treatment and does not indicate that *Akkermansia* could be a treatment.

Aside from the foregoing, Kaplan identifies Exhibit 1588 as "P. Turnbaugh, RYGB 16S Data, Notes (Aug. 29, 2011 to Nov. 26, 2011)," and Dr. Turnbaugh refers to Exhibit 1588 in regard to a sequencing analysis of August 29, 2011, but Kaplan does not direct us to any other evidence, such as the testimony of a non-inventor, that Exhibit 1588 is what Kaplan and Dr. Turnbaugh purport it to be. (*See* Kaplan Motion 3, Paper 362, 25; Turnbaugh Decl., Ex. 1588, ¶¶ 36–37.) Exhibit 1588 bears the date "8/29/11," but does not include a signature of either the creator of the document or of a witness. In the absence of authenticating evidence, we are not persuaded that Exhibit 1588 is evidence of a conception, or reduction to practice or that it is a document relevant to the time of Kaplan's priority case. Thus, in addition to not indicating that *Akkermansia* could be a treatment, Exhibit 1588 lacks authentication and corroboration.

Kaplan argues further that by August 30, 2011, Dr. Turnbaugh shared sequencing analysis demonstrating *Akkermansia* was significantly increased in the gut microbiome following RYGB surgery. (*See* Kaplan Motion 3, Paper 362, 9:20–11:11.) Kaplan highlights a page of Exhibit 1589, which Kaplan asserts is

presentation by Dr. Turnbaugh, dated August 30, 2011. (*See id.*) The highlighted page of Exhibit 1589 is reproduced below:



(P. Turnbaugh, Roux-en-Y gastric bypass surgery alters the colonic microbiota independently of diet and weight loss, Presentation (Aug. 30, 2011), Ex. 1589, 8.) The page is entitled "Relative abundance of major taxonomic groups post surgery," and includes three panels. The x-axis of each panel is labeled for treatments, including: "DIO," "RYGB_pre," RYGB_post," Sham_pre," "Sham_post,"

"WMS_pre," WMS_post," "LF," and "LF_RYGB." The y-axis of each panel indicates the percentage of a type of bacteria: *Clostridiales*, *Bacteroides*, and *Akkermansia muciniphila*. The panels include bars that indicate the percentage of bacteria for each treatment. The bars for "RYGB_post" and "Sham_post" for both the *Clostridiales* and *Akkermansia muciniphila* are highlighted with asterisks, which indicates "p<0.05 compared to pre-op samples." (*Id.*) The text under the panels states: "Clostridiales decrease and *A. muciniphila* increases in relative abundance post surgery in RYGB and Sham controls" and "No significant impact on Bacteroides." (*Id.*)

Kaplan argues that "[t]he *Akkermansia*-specific results shown above demonstrate an extremely low relative abundance of *A. muciniphila* pre-RYGB (second column from left, showing near zero relative abundance of *Akkermansia* before RYGB) and a marked, statistically significant (p<0.05) increase post-RYGB (third column from left, the olive-colored bar)." (Kaplan Motion 3, Paper 362, 10:6–11:2.) Kaplan acknowledges that the "Sham_post " bar, presumably indicating the percentage of *A. muciniphila* after sham surgery, was also statistically significant. (*See id.* at 11:2–4.) In addition, Kaplan acknowledges that Exhibit 1589 shows *Clostridiales* bacteria is significantly decreased and *Enterobacteriales* is significantly increased post-RYGB surgery. (*See id.* at, 10, fn 4 (citing Ex. 1589, 8–9).)

Kaplan argues that Dr. Turnbaugh found not only that RYGB surgery alters the gut microbiome, but also that two types of bacteria, including *Akkermansia* had a statistically significant increase after RYGB surgery. (*See* Kaplan Motion 3, Paper 362, 11:5–7.) According to Kaplan, "[t]hese results, together with the

inventors' observations that oral administration of substantially enriched *Akkermansia* resulted in weight loss in recipient mice compared to germ-free control mice, led the Kaplan inventors to conceive of *Akkermansia* as a microbe therapy for metabolic disorders." (*See* Kaplan Motion 3, Paper 362, 11:7–10.)

In support, Kaplan cites to Dr. Kaplan's testimony:

> Dr. Turnbaugh's findings provided evidence [referring previously to Exhibit 1589] that RYGB alters the gut microbiome and one of only two such microbes with a statistically significant increase after RYGB was *Akkermansia*. This, together with our observations that the oral administration of RYGB-associated gut microbiota (substantially enriched with *Akkermansia*) resulted in weight loss in germ-free recipient mice compared to germfree control mice, led us to identify *Akkermansia* as a microbe for therapeutic use.
>
> Specifically, from the analysis Dr. Turnbaugh presented on August 30, 2011, I understood that *Akkermansia* could be orally administered as a probiotic therapy to treat metabolic disorder. Of the large number of species/genera/orders analyzed, only two significantly increased in abundance following RYGB surgery: *Akkermansia* and *Enterobacteriales*. EX1589 (Aug. 2011 Presentation), 8-9. Therefore, at this time, we understood that either *Akkermansia* alone, *Enterobacteriales* alone, or *Akkermansia* and *Enterobacteriales* together could be orally administered as a probiotic therapy to treat metabolic disorder. We knew that the order *Enterobacteriales* comprised several pathogenic strains, for example, *E. coli.* Thus, I appreciated at least by August 31, 2011, that *Akkermansia* would be a preferred microbe to deliver as a probiotic.

(Kaplan Decl., Ex. 1624, ¶¶ 63–64 (footnote deleted).) Dr. Kaplan testifies that he identified *Akkermansia* as a treatment for metabolic disorder, but acknowledges that a combination with *Enterobacteriales* or *Enterobacteriales* alone could also be

administered as a treatment. According to Dr. Kaplan's testimony, *Akkermansia* was preferred because some strains of *Enterobacteriales* are pathogenic.

Kaplan also cites to Dr. Turnbaugh's testimony:

> Because we understood that the gut microbiome influences our metabolic health, including with respect to obesity, diabetes, and metabolic syndrome, and because we now had evidence that RYGB alters the gut microbiome, we recognized that we could treat metabolic disorders by influencing the composition and function of our gut microbiome through orally-administered compositions, such as probiotics including *Akkermansia*, to induce RYGB-associated alterations in the gut microbiome by, for example, triggering an increase in the abundance of *Akkermansia*. EX1589 (Aug. 2011 Presentation),
>
> More specifically, of the top 10 most abundant bacterial orders, my analysis showed that only two significantly increased in abundance following RYGB surgery—*Verrucomicrobiales* (i.e. *Akkermansia*) and *Enterobacteriales*—leading us to view each of these microbes (both alone and in combination) as key compositional components for oral administrations that would trigger changes in the gut microbiome similar to that seen after RYGB, and thus leading to beneficial metabolic effects, such as those seen in RYGB-R mice. *Id.*, 8-9. Moreover, among these options, we identified *Akkermansia* as the more advantageous microbe to include in oral administrations because we knew that the order *Enterobacteriales* includes several pathogenic strains (*e.g.*, members of the *E. coli* species), making it a less desirable option from a safety perspective. *See id.*, 9. Thus, by August 31, 2011, we appreciated that *Akkermansia* would be part of a therapeutic composition for the treatment of metabolic disease and had conceived the method of Count 1(a) by not later that this date.

(Turnbaugh Decl., Ex. 1625, ¶¶ 39–40 (footnote omitted).) Dr. Turnbaugh testifies that by August 31, 2011, he realized that *Akkermansia* would be part of a

therapeutic composition for the treatment of metabolic disease, even though both *Akkermansia* and *Enterobactiales* were significantly increased after RYGB surgery because *Enterobacteriales* includes several pathogenic strains.

Kaplan cites only to Exhibit 1589 and the testimony of inventors Kaplan and Turnbaugh in support of its argument that the inventors conceived of *Akkermansia* as a microbe therapy for metabolic disorders by August 31, 2011. (*See* Kaplan Motion 3, Paper 362, 11:7–11.) Neither Dr. Kaplan nor Dr. Turnbaugh cites to other evidence corroborating their focus on *Akkermansia* as a therapeutic composition to treat metabolic disorders. The pages of Exhibit 1589 that the inventors and Kaplan cite provided data showing the relative abundance of *Akkermansia* and other major bacterial taxonomic groups post surgery, but there is no mention of a treatment or therapy. *Akkermansia* is not described as being an effective therapy for metabolic disease or any other condition. Thus, the cited portion of Exhibit 1589 does not corroborate the inventor's testimony about their conception of a treatment with or therapeutic use of *Akkermansia*.

Furthermore, without corroboration, we are not persuaded that the inventors are not relying on hindsight in their testimony. *See EmeraChem*, 859 F.3d at 1346. The cited pages of Exhibit 1589 do not provide any information about pathogenic strains of *Enterobacteriales* and do not indicate that *Akkermansia* bacteria was preferred for any function over *Enterobacteriales* bacteria. Pages 8 and 9 of Exhibit 1589, cited by Kaplan and inventors Kaplan and Turnbaugh, do not indicate that at the relevant time the inventors thought the increase in concentration of *Akkermansia* could be therapeutically useful in any way. Even if the results highlighting the increase in *Akkermansia* support that the inventors may have had

reason to study *Akkermansia* or may have hoped that it would provide a treatment for metabolic diseases when administered orally, we would not be persuaded that the inventors conceived of an embodiment of the count at the relevant time because a research plan or general goal is not sufficient evidence of conception or reduction to practice. *See Burroughs Wellcome*, 40 F.3d at 1228.

Kaplan's argument for conception of an embodiment of the count continues by asserting that by August 31, 2011, the inventors knew gut microbes are altered by RYGB surgery, that the relative abundance of *Akkermansia* significantly increased in the gut microbiota after RYGB surgery, and that oral administration of cecal contents form RYGB surgery is a therapeutically effective treatment for metabolic disorders. (*See* Kaplan Motion 3, Paper 362, 11:12–18.) Kaplan argues that the inventors "put[] this information together" to conceive of the count, understanding that *Akkermansia* could be orally administered as probiotic therapy to treat a metabolic disorder. (*See id.* at 11:19–22.) In support, Kaplan cites the testimony of Dr. Liou, Kaplan, and Turnbaugh regarding the increased relative abundance of *Akkermansia* in the cecal contents of RGBY mice and the ability of oral administration of that cecal content to be a therapeutically effective treatment for metabolic disorders. (*See* Kaplan Decl., Ex. 1624, ¶ 65; Turnbaugh Decl., Ex. 1625, ¶ 41; Liou Decl., Ex. 1626, ¶ 42.)

For the reasons discussed above, including the lack of non-inventor, corroborating testimony and the absence of specific references to treatment with a therapeutically effective amount of *Akkermansia* in the relied upon documents, we are not persuaded that the inventors conceived of or reduced to practice a method of orally administering a composition to treat a metabolic disorder, wherein the

amount of *Akkermansia* bacteria in the composition administered is therapeutically effective.

Kaplan argues further that

> In particular, the inventors understood that *Akkermansia* could be orally administered as a probiotic therapy to treat metabolic disorder. **MF72 (EX1624, ¶64; EX1589, 8-9; EX1626, ¶42)**. From the results discussed above, it was reasonable for the inventors to conceive of the count, given their understanding that *A. muciniphila* is substantially enriched in the gut microbiota of mice after RYGB, the metabolic benefits of RYGB surgery are due—in large part—to RYGB-induced changes in the microbiome, and thus these metabolic benefits could be provided to recipient mice by orally administering microbiota substantially enriched in *Akkermansia* without surgery.

(Kaplan Motion 3, Paper 362, 11:20–12:4.) Again, the evidence that Kaplan cites in support is not persuasive. The cited testimony of Dr. Liou (Ex. 1626 ¶ 42), like the testimony of Drs. Kaplan and Turnbaugh, lacks corroboration of the oral administration of an amount of *Akkermansia* that is therapeutically effective to treat a metabolic disorder. Dr. Liou, like Dr. Kaplan, cites pages 8–9 of Exhibit 1589, but these pages do not refer to administration of *Akkermansia* as a treatment at all.

Furthermore, we are not persuaded by Kaplan's argument that it was "reasonable for the inventors to conceive of the count" given knowledge they had relating to the August 30, 2011, shared sequencing analysis that Dr. Turnbaugh shared. (Kaplan Motion 3, Paper 362, 11:22–12:4.) Kaplan cites the testimony of Dr. Goodman that

> the inventors could reasonably infer that the benefits of the surgery would be due, at least in part, to these microbiome changes, including

> the increase in *Akkermansia muciniphila*, and thus the metabolic benefits could be transferred to recipient mice by transferring the microbiota without the need to perform surgery. I believe that a POSA at the relevant time would agree with me with respect to the inventors' reasonable inferences.

(Third Goodman Decl., Ex. 1628, ¶ 28.) But neither Kaplan nor Dr. Goodman cites corroborated evidence of what the inventors were actually thinking at the time, specifically that they were thinking of treating a metabolic disorder by orally administering a therapeutic amount of *Akkermansia*. We have no reason to trust that Kaplan's argument and Dr. Goodman's testimony are not based on hindsight. (*See* Cani Opp. 3, Paper 371, 13:19–14:2 ("nothing in the documents shows that the inventors indeed had the necessary appreciation of the invention of the Count. Everything depends upon Dr. Goodman's hindsight attempt to find the invention in the experiments.").) Kaplan's arguments about what was reasonable to show conception or inferences do not persuade us that the inventors had a "definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech*, 802 F.2d at 1376.

Kaplan relies on the testimony of Drs. Maurice, Haiser, David, and Garrison for corroboration that the slides of Exhibit 1589 were presented by August 30, 2011. (*See* Kaplan Motion 3, Paper 362, 12:4–8 (citing Haiser Decl., Ex. 1629, ¶¶15–19; Maurice Decl., Ex. 1630, ¶¶ 13–19; Garrison Decl., Ex. 1631, ¶¶ 16–19; David Decl., Ex. 1632, ¶¶ 12–15).) Although these witnesses testify about personal knowledge of the presentation, they do not corroborate the inventor's testimony that based on the information in Exhibit 1589 they conceived a method

of orally administering a therapeutically effective amount of *Akkermansia* to treat a metabolic disorder. Dr. Haiser testifies that

> The August 2011 dates in the slides and in the filename are consistent with my memory, though the exact date is not firmly established in my memory, that this was around the time when Drs. Liou and Turnbaugh were discussing using oral administration of *Akkermansia muciniphila* to treat obesity and metabolic disorders.

(Haiser Decl., Ex. 1629, ¶ 18.) Similarly, Dr. Maurice testifies:

> The date "August 2011" on the first page of the presentation, as well as the August 30, 2011 indicated by the filename ("RYGB_8_30_2011") is consistent with my memory that Drs. Liou, Turnbaugh, and Kaplan were working on the oral administration of *Akkermansia muciniphila* for the treatment of metabolic disorders in mice around that time.

(Maurice Decl., Ex. 1630, ¶ 16.) Both Dr. Haiser and Dr. Maurice testify about discussion of treatment by orally administering *Akkermansia*, but it is not clear exactly what was discussed.[5]

Dr. Haiser testifies that his "memory of hearing discussions of using *Akkermansia muciniphila* to treat obesity and metabolic disorders around the August 2011 timeframe is consistent with the final slide of EX1589." (Haiser Decl., Ex. 1629, ¶ 19.) Dr. Maurice testifies that she recalls discussions and data regarding the presence of *Akkermansia* in the gut, including slides from Exhibit 1589. (Maurice Decl., Ex. 1630, ¶¶ 17–19.) But neither witness provides more

[5] Neither Dr. David nor Dr. Garrison testifies to any specific focus of the inventors on *Akkermansia* as a treatment at the time. (*See* Garrison Decl., Ex. 1631, ¶¶ 16–19; David Decl., Ex. 1632, ¶¶ 12–15.)

details of these discussions – for example neither testifies that discussions involved therapeutically effective amounts of *Akkermansia* or an amount of *Akkermansia* comprising 50% of a particular strain of *Akkermansia*. It is not clear how the slides of Exhibit 1589, which do not mention treatment involving administration of *Akkermansia*, support their testimony. Neither Dr. Haiser nor Dr. Maurice's testimony is specific enough to indicate that the inventors were discussing oral administration of a therapeutic amount of *Akkermansia* as required in the count. When we consider the totality of the evidence, including the lack of indication of oral administration of *Akkermansia* as a treatment in Exhibit 1589, we are not persuaded that Dr. Haiser's or Dr. Maurice's testimony corroborates the inventors' testimony about conception of the subject matter of the count.

Kaplan argues further that in October 2011, Dr. Harris and Dr. Liou drafted a grant application to Johnson & Johnson and that the subsequent "shift from Ethicon to Johnson & Johnson corroborates the inventors' prior conception of an oral therapeutic because Ethicon is primarily a device company, making Johnson & Johnson a better fit for this oral-therapeutic invention." (Kaplan Motion 3, Paper 362, 12:12–14.) Kaplan's argument does not persuade us that the Kaplan inventors conceived of an embodiment of the count by any date because even if Johnson & Johnson was interested in oral therapeutics, the reported "shift" does not indicate the inventors were considering oral administration of a therapeutically effective amount of substantially purified *Akkermansia* comprising 50% of a strain of *Akkermansia* to treat a metabolic disorder. Kaplan cites Exhibit 1606, an Innovation Disclosure Statement dated December 2011, and Exhibit 1607, an e-mail exchange between Drs. Harris, Liou, and Kaplan, dated October 2011, but

Kaplan does not identify discussion of oral administration of a therapeutically effective amount of *Akkermansia* to treat metabolic disease in either of these documents.

In opposition to Kaplan's argument, Cani argues that the only reference to *Akkermansia* in the Innovation Disclosure Statement is in regard to probiotic preparations that could alter the microbial ecology, wherein certain bacteria "may be of particular benefit," including *Clostridium*, *Bacteroides*, *Enterobacter*, and *Akkermansia*, as well as seven other bacterial taxa "to a lesser extent." (Innovation Disclosure Statement, Ex. 1606, 12; *see* Cani Opp. 3, Paper 371, 16:7–16.) Cani argues further that rather than highlighting *Akkermansia*, Exhibit 1606 includes the questions: "Can a subset of microbiota from the RYGB animal be identified that is driving this phenotype?" and "Is there a way to deliver RYGB contents or particular bacteria populations identified to be major players in host adiposity in non-germ free animals?" (*Id.* at 16:7–16 (citing Ex. 1606, 58, 65).)

We agree with Cani, that the portions of Exhibit 1606 Kaplan cites and the failure of Kaplan to identify discussion of oral administration of a therapeutically effective amount of *Akkermansia* to treat metabolic disease, undermines Kaplan's arguments of conception by August 2011. The lack of focus on *Akkermansia* in the Innovation Disclosure Statement of Exhibit 1606, which would presumably have highlighted the inventors' most important ideas, persuades us that the inventors had not yet conceived of using oral administration of a therapeutically effective amount of *Akkermansia* to treat metabolic disease by the date Kaplan asserts.

Neither Kaplan, nor Dr. Goodman explains how an increase in *Akkermansia*

indicated to the inventors an amount that is therapeutically effective as required in the 1(a) alternative of the count. Although the evidence Kaplan cites shows that the inventors achieved transfer of the cecal contents of RYGB mice to achieve weight loss and decreased adiposity, the evidence does not corroborate the inventors' testimony that they recognized *Akkermansia* was responsible for this effect. The Kaplan inventors showed that the amount of *Akkermansia* in RYGB cecal contents was increased over that of control, but the contemporaneous evidence Kaplan points to does not say anything about a therapeutic effect attributable to *Akkermansia,* much less of substantially purified *Akkermansia*, or a particular strain of *Akkermansia*.

C. Reduction to Practice

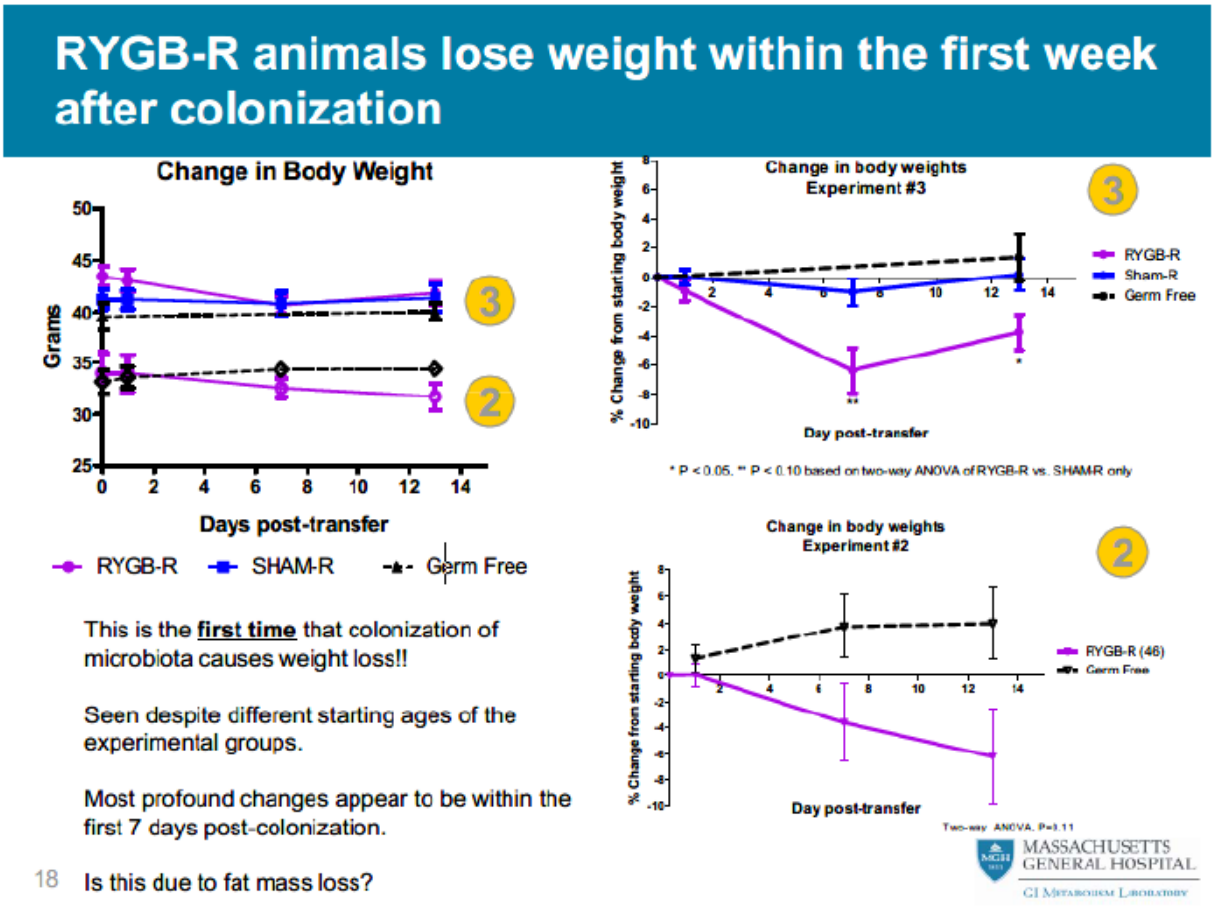
Kaplan argues that the inventors reduced to practice an embodiment of the count by November 2, 2011. (*See* Kaplan Motion 3, Paper 362, 13:13–17:10.) "In order to establish an actual reduction to practice, the inventor must prove that: (1) he constructed an embodiment or performed a process that met all the limitations of the interference count; and (2) he determined that the invention would work for its intended purpose." *Cooper v. Goldfarb,* 154 F.3d 1321, 1327 (Fed. Cir. 1998). Thus, we look for evidence that the inventors determined the therapeutic effectiveness of *Akkermansia* in an orally administered composition and determined that the composition would be able to treat a metabolic disorder.

1. "a therapeutically effective amount of bacteria comprising substantially purified *Akkermansia*"

As evidence of actual reduction to practice, Kaplan cites to page 56 of the

Interference 106,130

Innovation Disclosure Statement (Exhibit 1606), which is reported to show the results of cecal transfer experiments. (*See* Kaplan Motion 3, Paper 362, 13:23–14:7.) The slide cited by Kaplan in Exhibit 1606[6] is reproduced below.



The slide is entitled "RYGB-R [RYGB-Recipient] animals lose weight within the first week after colonization," and includes three panels entitled: "Change in Body Weight," "Change in body weights Experiment #3," and "Change in body weights

[6] Kaplan also cites to page 9 of Exhibit 1590, which appears to be the same slide. (*See, e.g.* Kaplan Motion 3, Paper 362, 14:4.)

Experiment #2." The panels compare results from "RYGB-R" (RYGB-Recipient), "SHAM-R" (SHAM-Recipient), and "Germ-Free" mice. The slide also includes annotations about colonization of the microbiota, although *Akkermansia* is not mentioned.

Kaplan characterizes the results as showing that after oral administration of cecal contents RYGB-recipient mice lost significantly more weight than Sham-recipient mice, which Kaplan concludes demonstrates that weight loss is caused by RYGB-specific colonization of the gut, rather than by the transfer procedure itself or colonization of the gut with non-RYGB cecal contents. (*See id.* at 13:18–23.) Kaplan argues:

> On November 2, 2011, a POSA would have recognized that the inventors reasonably appreciated the transferred RYGB-associated gut microbiome had the ability to promote metabolic health in highly relevant and widely used models of metabolic disease based on an analysis of the biometric data (body weights, cumulative food intake, and fat pad weights) obtained by Dr. Kaplan's group during experiments in which the RYGB-altered microbiome, with an increased abundance of *Akkermansia*, was used to inoculate germ-free mice**,** because the body weight of germ-free mice that received the RYGB-altered microbiome (RYGB-R mice) decreased significantly in the first two weeks after colonization, compared to the starting body weight on the day of inoculation, and because RYGB-R mice showed decreased adiposity compared to control mice. **MF89 (EX1628, ¶29; EX1590, 8-10; EX1606, 53, 56-57)**.
>
> From these results, a POSA would have recognized that the inventors reasonably understood a post-RYGB microbiome substantially enriched in *Akkermansia* contributes to the beneficial metabolic outcomes of RYGB, and reasonably inferred that beneficial metabolic outcomes (e.g., weight loss and decreased adiposity) can be triggered

> by colonization with a RYGB-altered microbiome with substantially enriched *A. muciniphila*. **MF90 (EX1628, ¶32)**.

(Kaplan Motion 3, Paper 362, 14:8–15:10.) Thus, Kaplan argues that one of ordinary skill in the art would have "recognized that the inventors reasonably appreciated" or "reasonably understood" that increased abundance of *Akkermansia* "contributes to the beneficial metabolic outcomes of RYGB," constituting a reduction to practice of the count. (*Id.*)

Dr. Goodman testifies in support of Kaplan's argument, stating

> The inventors demonstrated that germ-free mice inoculated with a DIO- and RYGB-altered microbiome substantially enriched in *Akkermansia* lost weight, showing that the RYGB-altered microbiome rescued recipient mice from the expected phenotype of weight and fat mass gain after colonization with a microbiome from a DIO mouse. From these results, it is my opinion that the inventors understood that alterations in the gut microbiome after RYGB, which include a dramatically increased abundance of *Akkermansia*, contribute to the beneficial metabolic outcomes of RYGB. It is also my opinion that the inventors would have inferred that these beneficial metabolic outcomes (*e.g.*, weight loss and decreased adiposity) can be triggered by colonization with RYGB-altered microbiome (*e.g.*, a microbiome enriched in *Akkermansia muciniphila*). Thus, the transfer experiments performed by the inventors using the germ-free mouse model provided reliable data about the suitability of the invention for the inventors' intended purpose. I believe that POSA at the relevant time viewing these results would share my opinions.

(Third Goodman Decl., Ex. 1628, ¶ 32.) According to Dr. Goodman, the inventors understood that increased abundance of *Akkermansia* contributes to the "beneficial metabolic outcomes of RYGB" and the inventors would have inferred that these

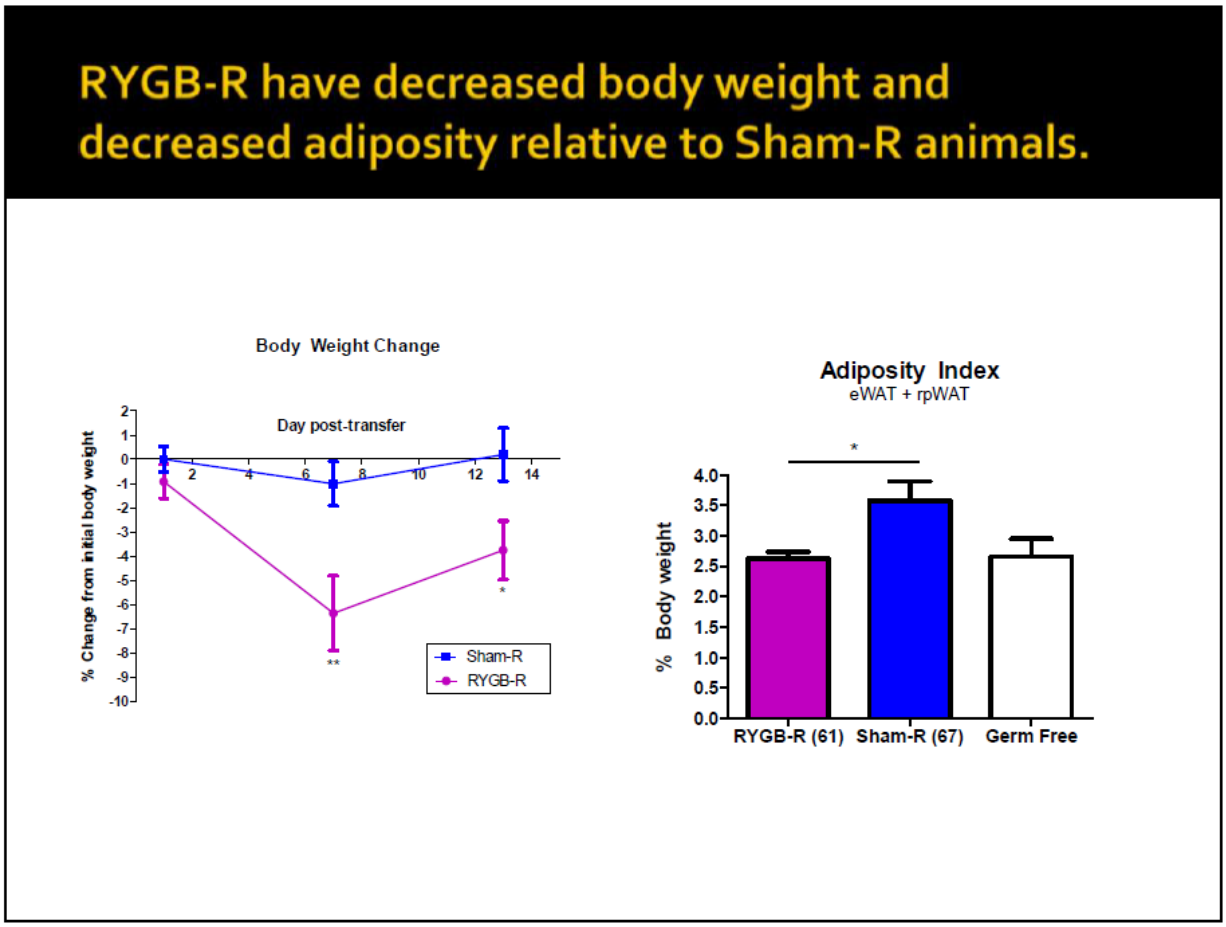
beneficial metabolic outcomes were "triggered by" a microbiome "enriched in *Akkermansia muciniphila*." (*Id.*)

Although Kaplan argues that the inventors would have inferred, recognized, or understood the benefits of a microbiome enriched in *Akkermansia*, Kaplan does not direct us to evidence that the inventors used a therapeutically effective amount of *Akkermansia* in an orally administered composition to treat a metabolic disorder. We are not persuaded that the cecal transfer composition used by the inventors included a therapeutically effective amount of *Akkermansia* or that the effects achieved were due to a therapeutically effective amount of *Akkermansia*. Inferences, recognition, and understandings do not persuade us that the inventors "contemporaneously appreciate[d] that the embodiment worked and that it met all the limitations of the interference count." *Cooper*, 154 F.3d at 1327 (actual reduction to practice requires proof of performing a process that meets all the limitations of the interference count).

Kaplan argues that Dr. Turnbaugh continued sequencing the gut microbiome of RYGB-R mice to confirm the composition of the colonizing microbes. (*See* Kaplan Motion 3, Paper 362, 15:11–13, citing Turnbaugh Decl., Ex. 1625, ¶ 44; November 21, 2011 Presentation, Ex. 1591, 10.) Dr. Turnbaugh testifies that the results of additional analysis for a third round of transfer experiments completed by November 21, 2011 "again confirmed that germ-free RYGB-R mice had significantly lower body weight (as a percent change from initial body weight) and decreased adiposity (as a percent of body weight) relative to germ-free Sham-R mice two weeks following inoculation." (Turnbaugh Decl., Ex. 1625, ¶ 44; *see also* Kaplan Decl., Ex. 1624, ¶ 72; Ex. 1625, ¶ 43; Liou Decl.,

Ex. 1626, ¶ 49.) Kaplan does not direct us to testimony from Dr. Turnbaugh that *Akkermansia* was present in a therapeutically effective amount in any of these experiments.

Kaplan cites to another slide in Exhibit 1591, reportedly with additional analysis, to argue further that RYGB-R mice lost more weight and had significantly decreased adiposity relative to Sham-R mice, indicating that "orally administering a composition comprising substantially enriched *Akkermansia* is an effective treatment for metabolic disorders." (*See* Kaplan Motion 3, Paper 362, 15:19–16:9 (citing Ex. 1591, 44).) This slide is reproduced below.



(Ex. 1591, 44.) This slide is entitled "RYGB-R have decreased body weight and decreased adiposity relative to Sham-R animals" and includes two panels: a line graph entitled "Body Weight Change" and a bar graph entitled "Adiposity Index." *Akkermansia* is not mentioned on the slide.

Kaplan cites to the testimony of Dr. Kaplan that "[t]aken in totality, the results demonstrated that oral administration of our RYGB-associated gut microbiota would be an effective treatment for metabolic disorders." (Kaplan Decl., Ex. 1624, ¶ 73; *see also* Liou Decl., Ex. 1626, ¶ 48; Ex. 1625, ¶ 45.) Dr.

Kaplan and the other inventors testify that the administered composition comprised "substantially enriched *Akkermansia*," wherein the *Akkermansia* would have been understood to be nearly all of any strain of *A. muciniphila*. (*Id.* at ¶ 74) None of the inventors, though, testify that the oral compositions of cecal contents transferred to the mice included an amount of *Akkermansia* that was therapeutically effective.

Kaplan summarizes the evidence of reduction to practice by November 2, 2011 and confirmed by November 21, 2011 as showing that oral administration of a composition comprising substantially enriched *Akkermansia* could be used to treat metabolic disorders. (Kaplan Motion 3, Paper 362, 16:11–17:1.) We agree that the evidence shows treatment of a metabolic disorder using a composition of bacteria that includes *Akkermansia*. But Kaplan's evidence does not demonstrate that this composition includes a therapeutically effective amount of *Akkermansia*. It is not clear that *Akkermansia* contributes to the effects of the transferred cecal contents on body weight or adiposity because the evidence also shows changes in other bacteria in the transferred cecal contents and those changes could have been the cause of the results in the absence of evidence to the contrary. In other words, the evidence relied on by Kaplan does not establish what changes in the cecal contents were responsible for the therapeutic effect. Accordingly, we are not persuaded that the evidence Kaplan cites demonstrates a reduction to practice of the 1(a) alternative of the count.

Kaplan argues further that the inventors simultaneously conceived and reduced to practice an embodiment of the count on November 2, 2011 and continued to work on the invention after the first reduction to practice between

November 2011 and January 2012. (*See* Kaplan Motion 3, Paper 362, 17:11–23:14.) The evidence that Kaplan presents, however, shows that *Akkermansia* was substantially enriched after RYGB treatment and in RYGB-R mice. (*See, e.g.,* Kaplan Motion 3, Paper 362, 19:20–20:5.) Kaplan fails, again, to direct us to evidence that the gut composition after RYGB treatment or the cecal contents transferred to mice contained a therapeutically effective amount of *Akkermansia* as required in the count, or that the inventors knew at the relevant time that a therapeutically effect amount of *Akkermansia* was responsible for the result. Thus, the evidence of work after the asserted first reduction to practice is not persuasive of later reductions to practice or conception of an embodiment of the count for the same reasons that the evidence of earlier reductions to practice are not persuasive. Namely, Kaplan fails to direct us to evidence of orally administering a therapeutically effective amount of *Akkermansia*.

Kaplan presents further evidence of asserted reductions to practice after November 2011, specifically Dr. Turnbaugh's continued analysis of the 16S tRNA gene sequencing data from donor and recipient cecal contents. (*See* Kaplan Motion 3, Paper 362, 19:20–23:12.) According to Kaplan, Dr. Turnbaugh found that the relative abundance of *Akkermansia* increased dramatically along the length of the intestine after RYGB surgery and that *Akkermansia* was significantly elevated in RYGB-R mice compared to Sham-R and WMS-R controls. (*See id.* (citing P. Turnbaugh Notes, Exs. 1592, 1593, Turnbaugh Dec., Ex. 1625, ¶¶ 46–50.) Even if Kaplan accurately reports the findings of Dr. Turnbaugh's analyses, this evidence is not sufficient to show reduction to practice of an embodiment of the count because, as with the evidence discussed above, it does not show that the

gut composition after RYGB treatment or the cecal contents transferred to mice contained a therapeutically effective amount of *Akkermansia* as required in the count, i.e., there is no evidence that correlates the therapeutic result to the increase in *Akkermansia*. The notation "Totally fascinating results, made new figures and wrote some text Looks like Akkermansia is the only group that's a lot higher in RYGB recipients!!!," which Kaplan attributes to Dr. Turnbaugh, does not state that a therapeutically effective amount of *Akkermansia* was orally administered or resulted in the treatment of a metabolic disorder. (Ex. 1593, 4; *see* Kaplan Reply 3, Paper 376, 7:16–19.) The notation merely suggests that there was more *Akkermansia* in RYGB recipients.

Cani argues that the experiments Kaplan presents as evidence are insufficient because one cannot be certain that *Akkermansia* was responsible for a therapeutic effect without testing it separately. (*See* Cani Opp. 3, Paper 371, 12:24–13:14.) In support, Cani cites Dr. Goodman's testimony:

> Q: So just to be clear, what you're saying is, is if you want to know whether Akkermansia is the material that's having an effect here, you would have to do experiments with Akkermansia by itself; is that right?
>
> Mr. Torczon: Objection. Asked and answered. Misstates.
>
> THE WITNESS: The – the way that I would look at this is that if I had, again, multiple experiments that allowed me to highlight a specific group of microbes as being the ones that show the common pattern among groups of subjects that have a common result, that I -- I would have a reasonable confidence that the groups of microbes that will have the -- effect that I'm looking for.
>
> In the case of this specific study, if a student came to me with data saying, you know, Verrucomicrobia are what our multiple experiments are pointing to, what I would tell them is, Get

> Akkermansia. And the reason for that is that at the time – and to some degree, also today, but certainly at the time, that was the microbe that anyone would go to within the Verrucomicrobia, because it was the one that – that we could get from ATCC, it had been described, the directions for culturing it were known.

(Goodman Depo., Ex. 2298, 147:18–148:22.) Thus, Dr. Goodman testifies that one should use *Akkermansia* itself to determine whether it causes an effect.

Cani cites further to a declaration Dr. Goodman filed in the European Patent Office. (*See* Cani Opp. 3, Paper 371, 12:27–13:10 (citing Goodman EPO Decl., Ex. 2264, ¶ 21).).) Specifically, Dr. Goodman testified:

> I have also reviewed the experiments disclosed in the patent (EP2753187), and in my opinion, they do not support, or provide evidence that administering *E. hallii* is useful for treating metabolic disorders, including insulin resistance and type 2 diabetes. Specifically, Example 1 concerns allogenic transfer of fecal material. Fecal matter will contain many different bacteria, from various species, genera and phyla. Example 1 attempts to correlate the changes in glucose metabolism measured to changes in the relative abundance of bacterial groups. This is flawed for many reasons. For example, the analysis does not consider that other non-bacterial components may contribute to any difference in glucose metabolism. Additionally, there is no way to determine which bacteria, if any, is responsible for any difference between the groups. It is also not determined whether the increase in certain bacteria reflects introduced bacteria or expansion of endogenous taxa. No evidence is provided to compare small intestinal levels of *E. hallii* or any other bacteria between healthy and obese subjects.

(Goodman EPO Decl., Ex. 2264, ¶ 21.) Thus, Dr. Goodman's opinion, albeit in regard to a different patent, was that experiments involving administration of fecal

material would not show that one species of bacteria is useful for treating metabolic disorders because the fecal material would contain other non-bacterial components and bacteria other than the species of interest, which could contribute to metabolic effects. (*See id*.)

Kaplan argues that Cani sets too high of a bar for reduction to practice. (*See* Kaplan Reply 3, Paper 376, 7:20–9:20.) According to Kaplan, Cani "demands that Kaplan prove *Akkermansia*, and only *Akkermansia*, is the sole ***causative*** agent of the entire therapeutic effect" and that "[t]he law does not require such an exacting standard." (Kaplan Reply 3, Paper 376, 8:5–8.)

We disagree that Cani's arguments reflect an inappropriate standard of proof for reduction to practice of the count in this proceeding as properly construed. Cani does not dispute that the composition of the count may include other bacteria, but Cani argues that the count requires *Akkermansia* to be therapeutically effective. (*See* Cani Opp. 3, Paper 371, 10:30–11:22.) Although Kaplan presents evidence that cecal transfers from RYGB mice could be used to treat metabolic disorders, Kaplan fails to direct us to evidence that the inventors showed *Akkermansia* was a causative agent. Even if the amount of *Akkermansia* was increased in the RYGB cecal compositions transferred, Kaplan does not direct us to experiments that demonstrated the effects of *Akkermansia*. From the evidence Kaplan presents, we are not persuaded the metabolic effects were not caused by other bacteria or conditions present in the cecal transfers from RYGB mice. As Dr. Goodman opined in his declaration to the European Patent Office, the transfer of fecal material includes many different bacteria and there is no way to determine which

bacteria, if any, is responsible for any effect. (*See* Goodman EPO Decl., Ex. 2264, ¶ 21.)

Kaplan argues that "it was the oral administration of that substantially enriched *Akkermansia* to the ***recipient*** mice that reduced the invention to practice and is the proper focus," but, as Dr. Goodman testified, substantial enrichment of *Akkermansia* in a composition is not sufficient to demonstrate that the *Akkermansia* was present in a therapeutically effective amount. (Kaplan Reply 3, Paper 376, 9:1–2.)

Kaplan argues that Cani inventor Dr. de Vos undermines Cani's arguments about the need for experiments using isolated *Akkermansia* by stating that "fecal transplantations of intestinal microbiota . . . not only provides causal relations but also shows considerable efficacy in treating various diseases." (Kaplan Reply 3, Paper 376, 9:6–14 (quoiting de Vos,[7] Ex. 1635, 2.) Dr. De Vos was referring to the therapeutic effects of the fecal transplants, as a whole, not of individual bacterial species within the fecal transplants. Accordingly, Kaplan's argument does not persuade us that the experiments highlighted by Kaplan show reduction to practice of the count.[8]

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[7] de Vos, *Fame and future of faecal transplantations – developing next-generation therapies with synthetic microbiomes*, 6 MICROBIAL BIOTECHNOLOGY 316 (2013).
[8] Kaplan argues that because Cani withdrew Dr. de Vos's testimony and because Dr. Goodman's testimony in the EPO proceeding (Ex. 2264) was about a patent allegedly invented by Dr. de Vos, we should give little weight to Cani's assertions. (*See* Kaplan Reply 3, Paper 376, 9:14–20.) Kaplan relies on Dr. de Vos's testimony, not Cani, and therefore we apply no negative inference. Nor do we discount Dr. Goodman's statements in the EPO proceeding because of the inventor of the challenged patent. In neither case does Kaplan present a substantive

2. "wherein the substantially purified *Akkermansia* comprises at least 50% of a strain of *Akkermansia*"

In addition to failing to persuade us that the inventors conceived or reduced to practice administering a composition with a therapeutically effective amount of *Akkermansia*, Kaplan also fails to direct us to evidence of orally administering a composition "wherein the substantially purified *Akkermansia* comprises at least 50% of a strain of *Akkermansia*," as required in the 1(a) alternative of the count.

According to Kaplan the term "strain" in the phrase "a strain" of the count must be taxonomically narrower than the genus limitation of *Akkermansia* in the phrase "substantially purified *Akkermansia.*" (*See* Kaplan Reply 3, Paper 376, 3:22–24.) Kaplan proposes that interpreting the term "strain" literally to mean "strain" or to mean "species" such as *A. muciniphila* would result in a narrower taxonomy than the genus *Akkermansia. (*See *id.*) Kaplan does not provide a reason why we should not adopt the literal interpretation of "strain."

We also adopt the literal interpretation of "strain" in light the knowledge in the art at the time. Specifically, Kaplan presents evidence that it was known there are multiple strains of *Akkermansia*, but that only one species, *A. muciniphila,* was known.[9] (*See* Kaplan Reply 3, Paper 376, 3:24–4:2.) Thus, according to Kaplan,

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argument that persuades us Cani is wrong to oppose Kaplan's evidence of reduction to practice based on the lack of evidence that *Akkermansia* is therapeutically effective.

[9] Kaplan asserts: "POSA understood 'strain' as used in Count 1(a). Dr. Hill testified the '870 patent did not define the term strain, but its [sic] would be understood by POSA. Dr. Hill testified POSA would have understood (1) *Akkermansia* to have multiple species, including *A. muciniphila*, and both had

if the term "strain" is interpreted to mean "species," as Cani proposes, the phrase "at least 50% of a strain of *Akkermansia*" would be meaningless in the count because the understanding in the art was there was only one species. (*See* Kaplan Reply 3, Paper 376, 3:24–4:4.) Kaplan's arguments and evidence persuade us to interpret the 1(a) alternative of the count to be limited to a composition comprising *Akkermansia*, wherein the *Akkermansia* comprises at least 50% of one of the strains of *A. muciniphila*. *See CCS Fitness,* 288 F.3d at 1366.

Kaplan fails to direct us to evidence of the percentage of any strain of *Akkermansia* in the fecal contents transferred in the experiments presented in its Motion 3 and fails to direct us to evidence that RYGB-R mice received a composition wherein the *Akkermansia* includes 50% of a strain of *Akkermansia* prior to November 2012, Cani's priority date. In the Reply Brief, Kaplan argues that "Cani also ignored Dr. Turnbaugh's 16s sequencing proved there was more than 50% of one species and one strain of *Akkermansia* in what was given (**MF44, 102, 105-106, 139; EX1625**, **¶¶50-51; EX1637, 61:13-66:13, 99:4-100:5, 148:17-156:22**)." (Kaplan Reply 3, Paper 376, 7:8–10.) But none of Kaplan's citations support the assertion that Dr. Turnbaugh proved that there was more than 50% of one strain of *Akkermansia*. Kaplan's Statements of Material Fact ("MFs") 44, 102, 105–106, 139) cite Dr. Turnbaugh's declaration, but not testimony that RYGB-R

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multiple strains; (2) strains are defined based on their genetic differences; and (3) strains and species are different." (Kaplan Reply Br. 3, Paper 376, II-35:8–12 (Statement of Material Fact 128) (citations omitted).) Because Kaplan asserts it to be a material fact that there are multiple strains of *Akkermansia*, we rely on that fact.

mice received a composition wherein the *Akkermansia* includes at least 50% of a strain of *Akkermansia*. (*See* Turnbaugh Decl., Ex. 1625, Turnbaugh Decl., Ex. 1625, ¶¶ 23, 47, 49, 50, 51.) Similarly, Kaplan's Statements of Material Fact cite Dr. Hill deposition, but Dr. Hill does not testify that RYGB-R mice received a composition wherein the *Akkermansia* includes at least 50% of a strain of *Akkermansia*. (*See* Hill Depo., Ex. 1637, **61:13-66:13, 99:4-100:5, 148:17-156:22.)**

More specifically, paragraphs 50 and 51 of Exhibit 1625, Dr. Turnbaugh's declaration, refer to the LEfSe algorithm and that he "observed that the resulting LEfSe plots showed that *Akkermansia* was significantly enriched in RYGB-mice as compared to Sham and WMS mice." (Turnbaugh Decl., Ex. 1625, ¶ 50, citing Ex. 1608.) Dr. Turnbaugh testifies further that the "LEfSe plot confirms that 99.9% of the sequencing reads assigned to OTUs within the *Akkermansia* genus from the RYGB recipient mice come from OTU178399. EX1623 (RYGB OTUs), 1 (rightmost value, showing average)," wherein "OTUs" are related sequences referred to as "operational taxonomic units." (*Id.* at ¶¶ 50, 51.) Neither Kaplan, nor Dr. Turnbaugh explains how an OTU relates to "a strain" of *Akkermansia* as recited in the count. In contrast, Dr. Hill testifies that there are no significant observations or annotations on Exhibit 1608 and that "Dr. Turnbaugh should have explained in the figure legend, that should have been associated with that figure." (Hill Depo., Ex. 1637, 155:1–3, *see, generally*, 148:17-156:22.)

After considering the evidence that Kaplan cites, we are not persuaded by Kaplan's assertion that "Dr. Turnbaugh's 16s sequencing . . . demonstrated there was more than 50% of one species and one strain of *Akkermansia* in the fecal

transplant administered to the germ-free recipient mice." (Kaplan Reply 3, II-36: 19–21, MF139.) We fail to find evidence cited by Kaplan in Motion 3 that demonstrates conception or reduction to practice of a composition, "wherein the substantially purified *Akkermansia* comprises at least 50% of one of the several strains of *Akkermansia,* as required in the count.

III. Conclusion

Kaplan fails to persuade us that its inventors conceived of or reduced to practice an embodiment of the count before Cani's priority date of November 19, 2012. Accordingly, we deny Kaplan Motion 3, arguing for priority as to the count.

Judgment will be entered separately.

Interference 106,130

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