

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MICROBIOTICA, LIMITED
Petitioner,

v.

BOARD OF REAGENTS, THE UNIVERSITY OF TEXAS SYSTEM
Patent Owner.

U.S. Patent No. 11,395,838

Issue Date: July 26, 2022

Title: Methods for Enhancing Immune Checkpoint Blockade Therapy by
Modulating the Microbiome

PGR2023-00026

**PETITIONER’S PRELIMINARY REPLY TO PATENT OWNER’S
PRELIMINARY RESPONSE**

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Patent Trial and Appeal Board

U.S. Patent and Trademark Office

P.O. Box 1450

Alexandria, VA 22313-1450

In Patent Owner’s Preliminary Response (“POPR”), Patent Owner (“PO”) ignores entirely interim controlling authority issued by the Supreme Court, mischaracterizes unrelated prior art as “cumulative” of Petitioner’s obviousness references, and relies on inapposite post-filed art to rebut Petitioner’s enablement arguments. Pursuant to the Board’s Order, Petitioner submits this Preliminary Reply to address these issues. PGR2023-00026, Paper 8 (Sept. 19, 2023).

A. The Supreme Court’s Amgen Decision Is Controlling Authority that Confirms the ’838 Patent Is Invalid for Lack of an Enabling Disclosure.

The Supreme Court’s interim decision in *Amgen v. Sanofi* is directly on-point with the issues raised in the Petition. PO’s failure to address this controlling authority – issued *after* the Petition was filed but *before* the POPR – is telling.

In *Amgen*, the claims were directed to an entire genus of antibodies (those binding to the “PCSK9 protein”) capable of blocking PCSK9 from impairing the body’s mechanism for removing LDL cholesterol from the bloodstream. *Amgen v. Sanofi*, No. 21-757, 598 U.S. __ (2023), slip op. at 5 (S.Ct. May 18, 2023).

Although the patent disclosed 26 exemplary antibodies, the claims read on potentially millions of antibodies that were not disclosed. *Id.* Applying the statutory command of §112(a) to the breadth of the claims, the Court held:

If a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent’s specification must enable a person skilled in the art to make and use the entire

class. In other words, the specification must enable the full scope of the invention as defined by its claims. **The more one claims, the more one must enable.**

Id. at 17 (emphasis added).

The Challenged Claims of the '838 Patent in this case purport to cover an equally unbounded scope as those found invalid in *Amgen*, except here, the specification provides even less support. As detailed in the Petition at pages 31-59 discussing the failure of the '838 Patent to satisfy the related requirements under 35 USC §112, including enablement, the Challenged Claims cover administering, through *any means* known to man, an *undefined* 'composition' of *unidentified bacteria* (at least some of which belong to the family Ruminococcaceae), with there being “*no limits* on the type of skin cancer that can be treated”, “*no list of ingredients or limits* on the type(s) of composition to be administered, how the composition can be administered, or even where the composition should be administered” and “*no identification* of the species of Ruminococcaceae bacteria that must be used, the concentration of such bacteria, or the purity of such bacteria.” Pet. 1-2 (citing Ex 1003, ¶¶ 57-59).¹ Nor does PO argue that the claims

¹ PO's repeated argument that the Petition only dedicates “4 sentences” to lack of enablement (EX-2028 9:17-20; 10:21-11:2; 14:6-8) is inaccurate as it ignores that

should be limited in any way. Under *Amgen*, the near limitless nature of the Challenged Claims would require a correspondingly limitless disclosure to satisfy the statutory command of §112(a). The scant and often times contradictory and inconclusive teachings in the '838 Patent, however, simply cannot support the extraordinary breadth of the Challenged Claims.

Nor can PO seek refuge in the experiments discussed in the specification, or the general skill in the art, to backfill the dearth of enabling disclosure. The *Amgen* Court identified two “qualifications” to the strict enablement requirement meant to balance the patent bargain; neither apply here. First, a specification need not describe with particularity how to make and use every embodiment within a claimed class if the specification identifies “some general quality... running through that class that gives it a peculiar fitness for a particular purpose.” *Amgen*, slip op. at 13-14 (citations omitted). Second, a patent claim can still be enabled if practicing the scope of claims requires only reasonable experimentation, as measured by the nature of the invention and the underlying art. *Id.* at 13-15.

In this case, however, the '838 Patent discloses only two experiments (Examples 3 and 4) wherein a “composition” (uncharacterized raw human feces)

the same factual basis on pp. 31-47 of the Petition supports all of Petitioner’s arguments under §112. *See* Pet. at p. 47.

was “administered” (by oral gavage) to a subject (healthy mice injected with a murine melanoma tumor model). Ex. 1001, ¶¶ 69-72. Neither example discloses any steps taken to characterize the specific bacteria, or the concentration of such bacteria, in the fecal samples or otherwise enrich the bacteria. *Id.* In other words, nowhere does the patent disclose *what* bacteria were administered, or even *how much* bacteria were administered, to these mice. Yet, just as in *Amgen*, PO seeks to monopolize *every* method of administering any composition containing at least some undefined quantity of Ruminococcaceae bacteria defined by a desired outcome – reducing or delaying the growth of a skin cancer tumor. As detailed in the Petition, there were dozens of species of bacteria thought to be in the Ruminococcaceae family², which means that the number of potential combinations and concentrations of compositions comprising such bacteria as recited in the

² At the time of filing, the species of bacteria falling “within the family Ruminococcaceae” was (and remains today) a moving target that renders the Challenged Claims indefinite. Ex. 1003, ¶145; *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1340-42 (Fed. Cir. 2003) (since glycosylation of uEPO is a “moving target” claim recitation of “glycosylation which differs from that of [uEPO]” was indefinite).

Challenged Claims is literally *without limit*. Pet. 23-24. Such a broad claim scope is no longer tenable under *Amgen*.

And like *Amgen*, PO failed to disclose any “quality” required by the claimed method that provides a “peculiar fitness for a particular purpose.” *Amgen*, slip op. at 16-17. Instead, Table 2 in the ’838 Patent shows that bacteria from the family Ruminococcaceae were found to be enriched in “non-responder” fecal samples or not significantly enriched in either the “responder” or “non-responder” fecal samples. Ex. 1003, ¶¶ 115, 130-133. Thus, even within the family Ruminococcaceae, the specification teaches that some bacteria had potentially beneficial effects, some had *no effect*, and others had *detrimental effects* on anti-tumor response. *Id.* at ¶ 135. Yet the Challenged Claims do not exclude these ineffective or detrimental bacteria from the litany of compositions PO claims “reduc[es] or delay[s] growth of a skin cancer tumor”. Nor does the specification teach any peculiar quality as to the claimed bacteria except that they are of the family Ruminococcaceae – one of the most common bacteria in human feces. EX-1014 p.255-256. Instead, a POSA is left to engage in “painstaking experimentation” to discover, *inter alia*, what bacteria are beneficial, at what concentrations, in what combinations, in which subjects, against which types of skin cancer, and through what route of administration, to achieve this intended result. “That is not enablement.” *Amgen*, slip op. at 17.

Worse yet, the difficulty of this “random trial-and-error discovery” is exemplified by PO’s admission that “the field of bacteria-based skin cancer treatment before September of 2016” was “riddled” with “unpredictability and inconsistent observations.” POPR 45-46 (*citing Osi Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019) (“hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art”); *see also Amgen*, slip op. at 17. And unlike the “road map” and “substitution strategy” left for future explorers in *Amgen* (which the Court nonetheless found was insufficient enabling disclosure), here PO left no map at all, because there are no practical limits on the claims and, thus, even the destination itself is undefined. No amount of “adaptation or testing” could lead a POSA to possession of the full scope of the Challenged Claims, much less any such experimentation that could be deemed “reasonable.”

Finally, PO’s argument that *Amgen* need not be addressed because it merely affirmed the lower court’s decision (EX2028, 8:10-10:20) ignores that the Supreme Court granted *certiorari* to clarify that claim scope **must** be commensurate with the specification’s disclosure. Now, courts across the country are following *Amgen*, finding functional genus claims, like the ones at issue here, invalid under §112. *See e.g., Baxalta Inc. v. Genentech, Inc.*, No. 22-1461, slip op. (Fed. Cir. Sept. 20, 2023) (following *Amgen*, claims to genus of antibodies performing a

function invalid §112); *Eli Lilly & Co. v. Teva Pharmaceuticals International GmbH*, 18-cv-12029 (D.Mass, September 26, 2023) (Dkt. No. 694) (relying in part on *Amgen*, granting JMOL that treatment method claims invalid under §112).

B. The Patent Owner Mischaracterizes the Art; For Instance, Honda and Tokyo are NOT Equivalent References.

PO argues that the Board should deny institution because the Petition relies on Honda (Ex. 1011) which it alleges is “the same or substantially the same art” as a reference submitted in an IDS, Tokyo, US2016/0193257 (Ex. 2012). POPR 28-32. PO’s analysis is incomplete and inaccurate.

As an initial matter, the two references are not related. Despite having a 2016 publication date, Tokyo claims a lineage to PCT/JP2012/007687, filed November 29, 2012, and further to provisional applications filed in March 2012 and December 2011. In contrast, Honda is published from a different application filed in April 2015, that claims priority to a provisional application filed in April 2014, three years after the claimed priority date of Tokyo. Besides being years after Tokyo, Honda does not claim priority to, or share disclosure with, Tokyo.

Nor is the disclosure in Honda that is cited in the Petition – *i.e.*, **the claims** – found anywhere in Tokyo. To the contrary, while the claims of Honda disclose a method of treating or reducing the severity of cancer in a patient through administration of a composition comprising bacteria from the family Ruminococcaceae, the claims of Tokyo are directed at treating autoimmune

diseases. Compare e.g., Ex. 1011, claim 12 (“*A method for... reducing the severity of ... cancer... comprising administering the composition of any one of the claims 1 to 9 [comprising, inter alia, **Ruminococcus sp. M-1, Ruminococcus sp. 16442** and/or **Ruminococcus gnavus**] to the individual*”) with e.g., Ex. 2012, claim 1 (“*A method of treating an autoimmune disease... comprising....*”).

While Tokyo was provided to the Examiner, along with more than 75 other references, the Examiner did not cite or otherwise rely on Tokyo to reject any claims. Likewise, the Examiner certainly could not have considered Honda in combination with the teachings of Gajewski and Miquel, as in the Petition.

C. The Patent Owner’s Reliance on Post-Filed Art is Misplaced.

PO’s attempt to rebut Petitioner’s enablement arguments with citation to two post-filing date publications is factually and legally incorrect. In order to rely on post-filed art to prove the “state of the art” at the time of filing, the experiments in the post-filed art must (i) be commensurate in scope with that disclosed in the application; and (ii) enable the full scope of the claims. See e.g., *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1376 (Fed. Cir. 1999) (to support enablement, post-filing successes must “follow[] the teachings of the specification” not “exercise substantial experimentation well beyond the broad concepts that appear in the specification”); *Amgen*, slip op. at 13. PO’s post-filed art fails on both score.

First, PO's allegation that the two post-filing publications, Baruch and Davar, "followed the FMT procedure described and claimed in the '838 Patent" is incorrect. POPR at 64-66. Even a cursory review of these references demonstrates that the "FMT procedures" employed by Baruch and Davar were vastly different from the mouse experiments in the '838 Patent and, thus, are not "commensurate in scope" with those in the '838 Patent. *Enzo Biochem*, 188 F.3d at 1376.

For example, in Baruch, patients received two forms of FMT: a colonoscopically administered FMT on Day 1, followed by oral capsules beginning on Day 12. All patients were pre-screened to show a demonstrated disease progression on at least one line of anti-PD-1 therapy, received antibiotic treatments prior to the first FMT, and were co-administered an anti-PD-1 therapy (nivolumab) every 14-days thereafter. Ex. 2019, at 1.

In Davar, patients received a single FMT administered colonoscopically on Day 0, along with co-administration of a different anti-PD-1 therapy (pembrolizumab) every 3 weeks thereafter. All of the Davar patients were primary refractory to anti-PD-1 therapy, meaning they had no prior response to anti-PD-1 alone or in combination with other agents. Ex. 2020 at 1.

In contrast, the mice studied in the '838 Patent received FMT of raw feces by oral gavage 3 times over 1 week. In some experiments, the mice were also orally administered a butyrate short-chain fatty acid. Ex. 1001 at 181:20-184:44.

Unlike Baruch or Davar, no oral capsules were administered, nor colonoscopic administration performed. Thus, the experimentation in Baruch and Davar is in no way “commensurate in scope” with that disclosed in the ’838 Patent and, thus, neither reference is relevant to the issue of enablement. *Enzo Biochem*, 188 F.3d at 1376 (post-filing art must follow teachings of the specification).

Second, even accepting Baruch and Davar to be relevant post-filed art (they are not), neither publication is sufficient to enable the full scope of the Claims. *See Amgen*, slip op. at 17 (“If a patent claims an ***entire class*** of subject matter, the specification must enable... the ***entire class***.”) (emphasis added). Here, neither publication discloses administering a “composition comprising an isolated or purified population of bacteria from the family Ruminococcaceae” in order to “reduc[e] or delay[] growth of a skin cancer tumor.” But even if they did, they do not enable a POSA to administer such a composition at any ***concentration imaginable***, using ***any technique imaginable***, to ***every vertebrate subject imaginable***, to reduce or delay the growth of skin cancer ***of any type imaginable***. Contrary to PO’s statement, it appears the only “similarities” between the ’838 Patent and PO’s post-filed art is that none of the FMT samples were characterized for bacterial composition or concentration and, thus, none can be used to determine which bacteria, or combinations of bacteria, potentially show beneficial results. Simply put, PO’s post-filed art cannot save the validity of Challenged Claims.

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Respectfully submitted,

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CERTIFICATION OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e), the undersigned certifies that on September 28, 2023, a complete and entire copy of Petitioner's Reply to Patent Owner's Preliminary Response was served by electronic mail to the Patent Owner's counsel at the following addresses:

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