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Gut check: microbiome patent update

By Matthew Kitces and Mark James FitzGerald, PhD

The most frequent question we receive regarding microbiome IP continues to be whether the broad patents issued in this space will stand up to validity challenge. In the U.S., the most common avenue for challenging the validity of an issued patent is when invalidity is raised as a defense by an accused infringer during enforcement litigation. However, because no live biotherapeutic products (LBPs) have yet been approved by the Food and Drug Administration, there have not been LBP product sales and there has not until very recently been any U.S. patent litigation in this space. As such, the field is still anxiously looking for an indication of how microbiome-related patents will fare when challenged for validity. This makes the ongoing Post-Grant Review (PGR) challenge of U.S. Patent No. 9,855,302, which relates to the co-administration of immune checkpoint inhibitors and Bifidobacteria for the treatment of cancer, very interesting indeed. An oral hearing in the case was recently held. Contributing attorney author Matthew Kitces attended the hearing and provides the following report.

The only independent claim of the '302 patent recites:

— 1. A method of treating cancer in a human subject comprising co-administering to the subject an immune checkpoint inhibitor and a bacterial formulation comprising bacteria of the genus *Bifidobacterium*.

PGR became part of U.S. patent law with the enactment of the America Invents Act, which became effective in 2012, and was touted as providing an efficient avenue to challenge patent validity in a Patent Office proceeding outside of enforcement litigation. In reality, PGR has rarely been used because under the Act, petitioners are estopped from being able to assert any issue raised or that reasonably could have been raised in a PGR proceeding as a defense if the PGR fails to invalidate the patent and petitioners are later sued for infringement of the patent.

Nonetheless, last year, Genome & Company (Petitioner) filed a petition to initiate a Post Grant Review process for U.S. Patent No. 9,855,302 ('302 patent), owned by the University of Chicago (Patent Owner). On the basis of the petition, the Patent Trial and Appeal Board formally instituted the PGR procedure designated PGR2019-00002 (*Genome & Company v. The University of Chicago*) against the '302 patent in April 2019.

The procedure generally involves written arguments, which can be supported by expert reports for both sides, as well as depositions of the experts, followed by an oral hearing before a PTAB panel of three judges, with a ruling on validity to be issued within 12 months of initiating the procedure.

Quick summary

At the January 15, 2020, Post Grant Review oral hearing for *Genome & Company v. The University of Chicago* (PGR2019-00002), both parties argued about the validity of the U.S. Patent No. 9,855,302 before Judges Mitchell, Snedden, and Schneider. Despite strong arguments from both parties, the hearing seemed to end up benefiting Petitioner's arguments of non-enablement and obviousness regarding all claims of the '302 Patent. A ruling will be issued by April 15, 2020.

Below, we discuss the arguments of the parties and the reactions of the panel in regard to the question of enablement. The obviousness arguments will be addressed in a second issue.

Pre-hearing background

Petitioner asserts that the independent claim is extremely broad in that it relates to all types of cancers being treated with any combination of any checkpoint inhibitor and any *Bifidobacterium*, along any route of administration. As such, Petitioner argues that the full scope of the claim is not fully enabled by the specification, which provides experimental data for only two types of cancer being treated by a particular checkpoint inhibitor and a particular cocktail of several *Bifidobacterium* species through one particular route of administration.

The Patent Owner asserts that sufficient disclosure is provided to permit a POSITA to practice the invention over its full scope, and that the Petitioner has failed to show any evidence that certain combinations of checkpoint inhibitors and *Bifidobacterium* would not work as expected.

Hearing overview

On January 15, 2020, the Patent Trial and Appeal Board heard arguments for this case. Lead Judge Susan Mitchell presided over the hearing, along with Administrative Patent Judge Sheridan Snedden and Administrative Patent Judge John Schneider.

Petitioner focused its allotment of time on three primary issues:

- the reliability of their expert testimony,
- the obviousness of the '302 patent's claims, and
- the lack of enablement provided for the breadth of the '302 patent's claims.

The Patent Owner used its time to primarily address:

- the burden of proof as it falls on Petitioner to prove lack of enablement rather than the Patent Owner to prove enablement,
- the framing of checkpoint inhibitors as a class, and
- the lack of expected success for combinations of the art cited in the Petitioner's obviousness arguments.

Overall, representatives for Petitioner and Patent Owner both seemed well prepared and persuasive, although Petitioner seemed quicker in providing strong and persuasive answers to the judges' questions. The judges asked good, probative questions of both parties, although a good deal more during the Patent Owner's oral argument.

- **Judge Mitchell** asked questions that seemed focused more on various technical details in each party's arguments, probing the parties to see how they react. It seemed that Judge Mitchell was more pleased with the Petitioner's answers than the Patent Owner's.
- **Judge Snedden** asked only a handful of questions throughout, primarily posing challenges to some of Petitioner's arguments. On at least one occasion, Judge Snedden did speak up to help clarify Patent Owner's answers to one of Judge Schneider's questions. However, Judge Snedden did seem to dislike Patent Owner's lack of caselaw support for some arguments.
- **Judge Schneider** asked a few clarification questions during Petitioner's arguments, but a good number of challenging questions to Patent Owner. Particularly, Judge Schneider asked the Patent Owner numerous times about whether they had any enablement support for any checkpoint inhibitors other than antibody checkpoint inhibitors.

Just based on the questions asked and tenor of the conversations, it seemed to this observer that Judge Schneider was leaning toward the Petitioner, Judge Snedden was on the fence but leaning slightly toward the Patent Owner, and Judge Mitchell was slightly leaning toward the Petitioner.

After the hearing was complete, it seemed to this observer that the Petitioner made a very strong case and backed it up with plenty of well-explained evidence, but the Patent Owner's arguments did not seem as strong or as clearly supported. While both sides did seem to have valid positions, this observer feels this hearing benefitted the Petitioner more than the Patent Owner.

Recap of arguments regarding expert testimony and enablement at hearing

Expert testimony

Petitioner used expert testimony for various assertions in its case. Patent Owner challenged the reliability of the expert at various points, so Petitioner addressed these issues quickly in its oral argument. Petitioner pointed to the expert's education and actual, clinical experience. After some quick questions, Judges Mitchell and Schneider seemed satisfied in the expert's clinical experience in actually managing treatment of cancer patients, including through the prescription of checkpoint inhibitors. Patent Owner did not address the expert's testimony much in its oral arguments.

Enablement

Petitioner argued that there are many different types of cancers, and that checkpoint inhibitors are defined very broadly by the '302 patent. Petitioner reiterated several times that the term "checkpoint inhibitor" was defined functionally by the '302 patent, such that it included proteins, polypeptides, antibodies, antigen-binding fragments thereof, and interfering nucleic acid molecules that would specifically bind to or otherwise inhibit expression or activity of an immune checkpoint protein. Early in Patent Owner's arguments, Judge Schneider asked if they had any disclosure in the '302 patent or any citations or other support anywhere that disclosed a checkpoint inhibitor that was not an antibody. The Patent Owner did not. Whenever Patent Owner turned to new art or citations about checkpoint inhibitors throughout the rest of the hearing, Judge Schneider would ask about whether that art taught non-antibody checkpoint inhibitors, to which the Patent Owner would respond in the negative. When pressed, Patent Owner could not point to whether there was any evidence ever showing that non-antibody checkpoint inhibitors worked.

An interesting point raised by the Petitioner that seemed to catch the attention of the judges was that several of the checkpoint inhibitors provided in a listing from claim 18 were not described in

the ‘302 patent and Petitioner was unable to find information about those checkpoint inhibitors elsewhere. When Judge Schneider later pressed the Patent Owner about the trouble finding some of the checkpoint inhibitors listed in claim 18, the Patent Owner was unable to provide any reference to the ‘302 patent or to any other literature to describe those checkpoint inhibitors, but suggested they could provide such citations later.

Petitioner also pointed out that the Patent Owner never cites to its own patent in order to support enablement. However, the Patent Owner counters this and other arguments by stating that the Patent Owner is not in a position to prove enablement, but rather that the Petitioner has failed to prove non-enablement. The Patent Owner argues that the Petitioner has failed to show any evidence that certain combinations of checkpoint inhibitors and *Bifidobacteria* would not work to treat cancer.

The Petitioner presented arguments about the sheer number of trials necessary to test each combination of checkpoint inhibitor and *Bifidobacteria*, which amounts to around 100,000 tests, or 1 million tests if you include different routes of administration. While this argument did not appear to receive a lot of favor, especially by Judges Snedden and Schneider, the argument Petitioner provided that the ’302 patent fails to provide any suitable guidance for how testing could be conducted, such as by providing a biomarker, seemed to be better received. The Petitioner also briefly went through some of the other *In re Wands* factors for undue experimentation, as supported by its expert.

The Patent Owner argued that the ‘302 patent described the invention sufficiently such that a POSITA would know how to practice the invention, and that despite the large number of trials necessary, a POSITA would have a reasonable expectation of success. The Patent Owner also attempted to argue that Petitioner failed to address any of the other factors for undue experimentation because the expert only provided assertions for the factors. Judge Schneider quickly pointed out that the expert provided evidence for each statement, but the Patent Owner nevertheless claimed it was only assertions. Again, Judge Schneider asked about non-antibody checkpoint inhibitors, and whether assessing them for use would require any undue experimentation, to which the Patent Owner asserted that they would be a member of the “checkpoint inhibitor” class, and thus would not require undue experimentation.

The Patent Owner argued that checkpoint inhibitors should be considered as a class, and therefore there is no need to provide support for each different type of checkpoint inhibitor. Judge Mitchell asked if there is any evidence that checkpoint inhibitors are interchangeable, but the Patent Owner did not cite any. Instead, Patent Owner’s arguments focused on showing that a wide variety of checkpoint inhibitors could be used to treat a wide spectrum of tumors. So, because the therapeutic responses are across a wide spectrum of cancers, Patent Owner asserted that a POSITA would expect all cancers to be treatable by one or more checkpoint inhibitors. Patent Owner also pointed to an FDA approval of checkpoint inhibitors that does not limit the checkpoint inhibitors to any specific tumor type, thus supporting the assertion that checkpoint inhibitors should be treated as a class. Petitioner argued that whether or not a checkpoint inhibitor is a class has nothing to do with the claims because the claims did not refer to a class. Rather, the ‘302 patent claimed checkpoint inhibitors functionally, such as in claim 15, defining the checkpoint inhibitor in terms of binding to an immune checkpoint protein.

An interesting argument by the Patent Owner was that there are mechanisms of action of checkpoint inhibitors that go beyond the Petitioner’s expert’s testimony. Specifically, the expert

focused on the signal disruption of checkpoint inhibitors. However, Patent Owner argued that checkpoint inhibitors also alter the overall balance of immunostimulatory and immunosuppressive activity in the system. The Patent Owner seemed to use this argument to show how checkpoint inhibitors, as a class, could be used to treat all cancers.

Burden of proof

The Patent Owner began its oral argument addressing how the Petitioner has failed to meet its burden of proof in arguing non-enablement. Judge Schneider pushed about the missing disclosure of certain checkpoint inhibitors in claim 18, to which the Patent Owner initially responded that the Petitioner failed to show evidence that any of those checkpoint inhibitors would not work. Judge Schneider quickly responded saying that the specification must enable all claims and Judge Mitchell stated that Patent Owner's position would "turn the case over on its head" because the full scope of the claims must be enabled by the specification and the Petitioner does not have to prove something failed. Judge Snedden asked for any caselaw to support Patent Owner's assertions about the Petitioner needing to prove failure, but the Patent Owner was unable to provide any on the spot. Judge Snedden asked if the Patent Owner's position was that in order to decide enablement, they must determine if the Petitioner met its burden, to which the Patent Owner responded yes. The judges did not appear to agree with the Patent Owner's line of argument regarding the burden of proof, especially with the lack of caselaw to support its position.

For more information on the content of this alert, please contact your Nixon Peabody attorney or:

- Matthew Kitces at **mkitces@nixonpeabody.com** or 202-585-8026
- Mark James FitzGerald, PhD at **mfitzgerald@nixonpeabody.com** or 617-345-1058
- David S. Resnick at **dresnick@nixonpeabody.com** or 617-345-6057