Gut check: Microbiome patent update

By Mark J. FitzGerald and David S. Resnick

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Recently issued microbiome-related patents:

U.S. Patent 9,839,655

— Titled: Compositions Comprising Bacterial Strains
— Assignee: 4D Pharma Research Ltd.
— Issued: December 12, 2017

Claim of interest:

1. A pharmaceutical composition that comprises:
   a) a therapeutically effective amount of a bacteria strain of the species Enterococcus gallinarum deposited under accession number NCIMB 42488; and
   b) a pharmaceutically acceptable excipient, diluent or carrier;
   c) wherein said therapeutically effective amount of said bacteria strain is an amount sufficient for treating cancer in a subject, and
   d) wherein said bacteria strain is lyophilized.

This claim is of interest for reciting a pharmaceutical composition comprising a specified strain of bacteria in an amount sufficient for treating cancer. Of note, the specification included demonstration of reduced tumor size in four different murine tumor models, which is likely why the issued claims broadly refer to “cancer,” as opposed to specific types of cancer.

The application was prosecuted under the Track One expedited examination procedure.
There were no prior art issues raised by the Examiner. The claims as filed recited the “wherein said bacteria strain is lyophilized” limitation in the alternative, and faced a §101 patent-eligible-subject matter rejection that was overcome by making the lyophilization limitation a required element. A §112 written description rejection was overcome by limitation to the specified strain, which was also supported by a biological deposit.

Finally, the specification includes significant detail regarding the carbohydrate fermentation profile of the active strain, which provides a potential alternative or additional approach to 16S sequence similarity for describing closely related microbes likely to share similar function.

U.S. Patent 9,835,632
— Titled: Biomarker Panel for Assessment of Mucosal Healing
— Assignee: Nestec S.A.
— Issued: December 5, 2017

**Claim of interest:**
— 1. A method for predicting the likelihood or extent of intestinal mucosal healing in a subject using an endoscopic surrogate measurement score, the method comprising:
   a) measuring the concentration or level of each of a plurality of biomarkers in a sample obtained from the subject, wherein the plurality of biomarkers consists of a combination of hepatocyte growth factor (HGF), betacellulin (BTC), an anti TNFα drug trough level and vascular cell adhesion molecule 1 (VCAM-1);
   b) comparing the concentration or level of the plurality of biomarkers to a cut-off value for each biomarker to assign an index value to the concentration or level of each biomarker;
   c) determining a cumulative biomarker score by applying an algorithm to the index values to determine said endoscopic surrogate measurement score; and
   d) predicting an increased likelihood or the extent of intestinal mucosal healing in the subject based on the endoscopic surrogate measurement score.

Claims of this patent are not strictly related to the microbiome, although several of the additional serum biomarkers described in the specification are components of the enteric microbiota. This claim is flagged here more for its being a straight diagnostic claim allowed in the post-Myriad/Myo age of § 101 patent-eligible subject matter. The Examiner indicated that the cumulative biomarker score, which combines four different biomarkers via an algorithm for diagnosis is an active step that is not well-known, conventional or routine in the field.

U.S. Patent 9,833,483
— Titled: Composition for Inducing Proliferation or Accumulation of Regulatory T Cells
— Assignee: The University of Tokyo
— Issued: December 5, 2017

**Claim of interest:**
— 1. A pharmaceutical composition, comprising a purified bacterial mixture of six or more live bacterial strains belonging to Clostridium clusters IV and/or XIVa, wherein the bacterial mixture induces proliferation and/or accumulation of regulatory T cells, wherein the
bacterial cells are isolated from a human, and wherein the pharmaceutical composition is formulated for delivery to the intestine.

This claim is of interest in that it covers a composition comprising a purified bacterial mixture of six or more live bacterial strains defined only as belonging to Clostridium clusters IV and/or XIVa and having the functional characteristic of inducing proliferation/accumulation of T\textsubscript{reg} cells. No specific strains are recited. The claims encompass naturally occurring strains isolated from a human, but require a formulation for delivery to the intestine, which arguably defines § 101 patent-eligible subject matter.

This patent was prosecuted under the Track One expedited examination procedure, and encountered only obviousness-type double patenting issues related to prior-filed and copending or issued applications claiming priority to the parent Japanese PCT application.

A granted European family member of this patent, EP2575835 B1, includes use-limited composition claims of largely similar, but slightly narrower scope, and is the subject of current Opposition proceedings in the European Patent Office (see below).

**U.S. Patent 9,855,302**

- Titled: Treatment of Cancer by Manipulation of Commensal Microflora
- Assignee: The University of Chicago
- Issued: January 2, 2018

**Claim of interest:**

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*.

This claim is of interest for its recitation of a method of treating cancer, generally, by co-administering a checkpoint inhibitor and a formulation broadly comprising bacteria of the genus *Bifidobacterium*. While the issued claims require co-administration of the checkpoint inhibitor and the bacterial preparation, it is interesting to note that, like the 9,839,655 patent discussed above, an effect of bacteria alone on tumor growth, tumor-specific T cell response and T cell infiltration into tumors is demonstrated in the specification.

The application was prosecuted under the Track One expedited examination procedure. The primary issue raised was obviousness over a combination of a reference describing the use of Bifidobacteria to treat autoimmune disease with a reference teaching the use of checkpoint inhibitors to treat cancer. The Examiner argued that both *Bifidobacterium* and checkpoint inhibitors suppress the immune response, so it would be obvious to combine them. After considerable effort, the Applicant succeeded in (properly!) persuading the Examiner that checkpoint inhibitors inhibit an inhibitory pathway, so as to *promote*, rather than inhibit an immune response.

**U.S. Patent 9,883,692**

- Titled: Nutrition with Non-Viable Bifidobacterium and Non-Digestible Oligosaccharide
- Assignee: N.V. Nutricia
- Issued: February 6, 2018
Claim of interest:

1. A nutritional composition, which has a pH between 5.5 and 8, comprising:
   a) a first and/or a second non-digestible oligosaccharide each having a degree of polymerization of 2 to 200, wherein the first non-digestible oligosaccharide is a transgalacto-oligosaccharide and the second non-digestible oligosaccharides is a fructo-oligosaccharide;
   b) non-viable Bifidobacterium breve from strain M-16V or I-2219 in an amount equivalent to 106 to 1013 colony forming units B. breve per gram dry weight of the nutritional composition, wherein viable Bifidobacterium breve bacteria are present in an amount that is below their detection limit as measured by plating; and
   c) cow’s milk protein.

This claim is of interest in being drawn to a nutritional composition that includes non-viable Bifidobacteria of either of the specific strains recited, in combination with the components recited in clauses (a) and (c). The specification emphasizes the surprising result of treating or preventing food allergy or other atopic diseases using non-viable, as opposed to viable, pro-biotic Bifidobacteria. Interestingly, one of the more contentious issues encountered during prosecution was how to define equivalents of CFUs for a non-viable bacterial preparation.

In sum…

The link between cancer and the microbiome continues to come up in newly issued patents, and it’s interesting from a scientific standpoint that not only response to checkpoint inhibition, but also effects on tumor growth without additional agents is related to microbiome bacteria. The potential benefits of microbes, dead or alive, and apart from metabolic products produced by living bacteria, continue to expand, as do patents relating to such benefits.

Challenges to microbiome patent validity: Patent oppositions

A question that comes up repeatedly in discussions regarding the scope of claims issuing in the microbiome space is whether any of the broad claims issued have been challenged in court or in other proceedings.

We are not yet aware of completed litigation regarding microbiome-related patents in the U.S., but a number of Opposition proceedings have been instituted and/or completed in the European Patent Office (EPO). While Post-Grant Proceedings and Inter Parties Reviews are relatively new avenues for patent challenge in the U.S., Oppositions have long been available and are frequently used in the EPO. Quite apart from the individual outcomes, it’s instructive to see how microbiome-related patents might be successfully dismantled. We comment on several decided and pending Oppositions here, and will provide further details as things develop.

EP 2211879 B1

- Titled: Probiotic Compositions and Methods for Inducing and Supporting Weight Loss
- Assignee: Brenda E. Moore
- Patent Granted May 7, 2014
- Opposition Status: Decided—Patent invalidated; decision under appeal
Representative claims:

1. A probiotic composition comprising a bacteria selected from the genus Bacteroides and a pharmaceutically acceptable carrier.

2. The probiotic composition according to claim 1 wherein said bacteria is selected from the group consisting of Bacteroides thetaiotaomicron, B. adolescentis, B. fragilis, B. vulgatus, B. distasonis, B. ovatus, B. stercoris, B. merdae, B. uniformis, B. eggerithii and B. caccae.

This patent was opposed by Danisco and by DuPont Nutrition. The “probiotic composition” was interpreted by the EPO during examination as one providing weight loss as a probiotic function. That is, the problem to be solved by the claimed invention is providing weight loss. Under EPO practice, when a claimed composition or method does not solve the problem it purports to solve, the Applicant has not provided an inventive step over the prior art. During the Opposition proceedings, despite post-filing data provided by the patentee, the Opposition Division found a lack of inventive step on the grounds that the claimed composition does not solve the problem of promoting weight loss (it is noted that the Opposition Division made a distinction between weight loss and a change in fat content). Potentially contributing to the panel’s decision were Opponents’ arguments that some strains encompassed by the independent claim actually promoted weight gain.

The patentee has proposed amendment of the claims in the pending appeal proceeding—note that the ability to amend claims during post-grant proceedings and appeal is in contrast to U.S. practices. In one of two alternative proposals, the patentee has proposed to recite lyophilized bacteria of the species noted in issued claim 2, with a pharmaceutically acceptable carrier. In the other, the patentee has proposed reciting certain amounts of lyophilized B. thetaiotaomicron cells as a powder, with lactose, corn starch and magnesium stearate, in a capsule.

Where the general perception is that overly broad microbiome-related claims have been issued in some instances, it would not be surprising to see even further amendment be necessary to rescue claims during the appeal.

EP 2431044 B1

- Titled: Probiotics to Influence Fat Metabolism and Obesity
- Assignee: Arla Foods
- Patent Granted January 13, 2016
- Opposition Status: Decided—Patent revoked July 11, 2017

Representative claims:

1. Use of at least one probiotic bacteria for lowering weight gain, wherein the at least one probiotic bacteria is selected from the group consisting of Lactobacillus casei F19 (LMG P517806), Lactobacillus acidophilus (NCFB 1748) and Bifidobacterium lactis Bb12 (DSM 15954) with the proviso that the use of said bacteria is not for therapeutic treatment.

2. Use of at least one probiotic bacteria for increasing satiety, wherein the at least one probiotic bacteria is selected from the group consisting of Lactobacillus casei F19 (LMG P1017806), Lactobacillus acidophilus (NCFB 1748) and Bifidobacterium lactis Bb12 (DSM 15954) with the proviso that the use of said bacteria is not for therapeutic treatment.

3. Use of at least one probiotic bacteria for prolonging satiety, wherein the at least one probiotic bacteria is selected from the group consisting of Lactobacillus casei F19 (LMG P15
4. Use of at least one probiotic bacteria for reducing food intake, wherein the at least one probiotic bacteria is selected from the group consisting of Lactobacillus casei F19 (LMG P-17806), Lactobacillus acidophilus (NCFB 1748) and Bifidobacterium lactis Bb12 (DSM 15954) with the proviso that the use of said bacteria is not for therapeutic treatment.

5. Use of at least one probiotic bacteria for reducing fat deposition, wherein the at least one probiotic bacteria is selected from the group consisting of Lactobacillus casei F19 (LMG P-17806), Lactobacillus acidophilus (NCFB 1748) and Bifidobacterium lactis Bb12 (DSM 15954) with the proviso that the use of said bacteria is not for therapeutic treatment.

6. Use of at least one probiotic bacteria for lowering storage of abdominal fat, wherein the at least one probiotic bacteria is selected from the group consisting of Lactobacillus casei F19 (LMG P-17806), Lactobacillus acidophilus (NCFB 1748) and Bifidobacterium lactis Bb12 (DSM 15954) with the proviso that the use of said bacteria is not for therapeutic treatment.

This patent was successfully opposed by Nestec. Opposition was, in part, on the grounds that there was no evidence that each of the three bacterial strains recited in each of the noted independent claims is able to provide all of the claimed benefits. In particular, the Opponent pointed to B. lactis Bb12, arguing that there is no evidence provided for the ability to lower weight gain, but that there is evidence that that strain cannot achieve that effect. As such, the Opponent argued that the claimed methods do not plausibly achieve the outcome recited.

EP 2234627 B1

- Titled: Prevention of Opportunistic Infections in Immunocompromised Subjects
- Assignee: Nestec
- Patent Granted May 25, 2016
- Opposition Status: Pending

Claim 1:

- A composition suitable for use in the prevention of opportunistic infections in immunocompromised individuals comprising a probiotic Bifidobacterium lactis, Bifidobacterium infantis, Bifidobacterium breve or Bifidobacterium longum and a fucosylated oligosaccharide selected from the group comprising 2'-fucosyllactose, 3 Tucosyllactose, difucosyllactose, lacto-N-lucopentaose, lacto-N-fucohexaose, fucosyllacto-N-hexaose and fucosyllacto-N-neohexaose.

This Nestec patent is challenged by a number of Opponents, including Abbott and N.V. Nutricia, on the basis of lack of novelty and/or inventive step, as well as sufficiency of disclosure. In particular, the Opponents assert that the claims as granted encompass human milk. The patentee has proposed a narrowing amendment to address this ground of challenge.

Oral proceedings are set for July 10–11, 2018, although several parties have requested an alternative date.

EP 2575835 B1

- Titled: Compositions for Inducing Proliferation or Accumulation of Regulatory T Cells
Assignee: University of Tokyo
Patent Granted October 19, 2016
Opposition Status: Pending

Claim 1:
A composition for use in a method of treating or preventing a disease selected from infectious disease, autoimmune disease or allergic disease in an individual, the composition comprising, as an active ingredient, bacteria comprising spore-forming bacteria belonging to Clostridium clusters IV and XIVa in combination, which combination induces proliferation or accumulation of transcription factor Foxp3-positive regulatory T cells in said individual.

Opponents can choose to remain anonymous. This patent is opposed by a number of anonymous parties, as well as Nestec and Seres Therapeutics. The patent is challenged on grounds of lack of novelty and obviousness/lack of inventive step in view of a number of patent and non-patent references, as well as insufficiency of disclosure, and amendments adding new matter. Challenges regarding the disclosure include arguments that the specification does not demonstrate treatment of infectious disease generally, and that the specification does not describe the combination of spore-forming bacteria of Clostridium clusters IV and XIVa.

Response by the patent owner is due by February 25, 2018.

In sum...
...patents perceived by some parties as overly broad are being successfully challenged in the EPO.

Some upcoming microbiome-related conferences/webinars:

Microbiome Data to Knowledge
— March 16, Seattle, WA
— Click here for more information

4th Annual Translational Microbiome Conference
— April 18–20, Boston, MA
— Mark FitzGerald and David Resnick of Nixon Peabody LLP and Caroline de Mareuil-Villette of Icosa will present a workshop on IP at the conference
— Click here for more information

Cancer Microbiome Congress
— May 8–9, Boston, MA
— Click here for more information

For more information on the content of this alert, please contact your regular Nixon Peabody attorney or:
— Mark J. FitzGerald at mfitzgerald@nixonpeabody.com or 617-345-1058
— David S. Resnick at dresnick@nixonpeabody.com or 617-345-6057