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## Gut check: microbiome patent update

By Mark J. Fitzgerald and David S. Resnick

Despite challenges imposed by U.S. patent law regarding naturally-occurring organisms and their products, patents relating to the microbiome and microbiome-based therapeutics are issuing from the U.S. Patent and Trademark Office. Issues encountered and the strategies used to overcome them are illustrated by the following selected examples of recently issued patent claims.

### U.S. Patent 9,603,878

- Issued March 28, 2017
- Titled “Probiotic and prebiotic compositions, and methods of use thereof for treatment and prevention of graft versus host disease”
- Assignee: Evelo Biosciences, Inc. (Cambridge, MA)
- Claim of Interest: A **method of treating or reducing the likelihood of** development of **graft versus host disease (GVHD)** in a subject receiving a transplant, comprising **administering to the subject** a probiotic composition comprising **an isolated, human-derived population of anti-inflammatory bacterial cells**, wherein said population **comprises three or more strains of anti-inflammatory bacteria capable of increasing secretion of Interleukin 10 (IL-10)** by human peripheral blood mononuclear cells (PBMCs) **in vitro**, and **wherein the population of anti-inflammatory bacterial cells increases IL-10 secretion by human PBMCs by at least 80% or more relative to each strain individually**, such that GVHD is treated or the likelihood that the subject develops GVHD is reduced.

This claim is notable for at least two reasons: (i) the independent claim includes *no reference to any specific species or strain of probiotic bacterial cells*; and (ii) the *probiotic strains are defined functionally* by their ability to increase IL-10 secretion by human PBMCs. Note that the claim requires synergy in IL-10 induction between the three or more strains of bacteria—the requirement for synergy between three or more strains was added by amendment during prosecution, along with a declaration demonstrating synergy between certain combinations, and was instrumental in overcoming an obviousness rejection based on the effects of single strains. As one might expect, dependent claims do include reference to specific species of bacteria.

While this patent demonstrates that broad claims are achievable in this arena, at 272 pages as issued, including 32 figures, this patent illustrates the benefits of including detailed disclosure and real data in the application.

The application was prosecuted under the Track One accelerated examination procedure.

### **U.S. Patent 9,567,361**

- Issued February 14, 2017
- Titled “Use of purified 2'-fucosyllactose, 3-fucosyllactose and lactodifucotetraose as prebiotics”
- Assignee: Glycosyn LLC (Woburn, MA)
- Claim of interest: A **method for stimulating the growth of an exogenously administered probiotic bacterium** in a gastrointestinal tract of a mammalian subject, **comprising: administering to said subject a composition comprising an oligosaccharide**, wherein **said oligosaccharide consists of (a) purified 2'-fucosyllactose (2'-FL), (b) purified 3-fucosyllactose (3-FL), (c) purified lactodifucotetraose (LDFT) or (d) a combination thereof**, wherein the **composition further comprises a probiotic bacterium** selected from the group consisting of *Bifidobacterium bifidum*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Bacteroides vulgatus*, *Lactococcus lactis*, and *Streptococcus thermophilus*, wherein said 2'-FL, said 3-FL, or said LDFT is at least 95%, 98%, or 99% pure, and **wherein said oligosaccharide selectively stimulates the growth of said probiotic bacterium**.

This claim relates to the use of particular classes of oligosaccharide prebiotics known to be present in human milk to promote the growth of exogenously administered probiotics. The USPTO cited prior art teaching that 2'-fucosyllactose was known to promote the growth of *Bifidobacteria* in support of an obviousness rejection. However, the applicants pointed out that the primary reference itself taught that only four *Bifidobacterial* species are stimulated by this oligosaccharide, and that other species do not see this effect. This teaching away permitted this claim, which recites other specific species, to issue over the prior art.

A recently filed continuation application is not yet publicly available, but likely includes composition claims drawn to a combination of the probiotic bacterial species and the milk oligosaccharides. Despite the oligosaccharides and the bacterial species being natural products, such combination, or variations of it, may provide an avenue to composition coverage that avoids rejection for encompassing non-patent-eligible subject matter under §101 of the patent statute.

### **U.S. Patent 9,596,876**

- Issued March 21, 2017
- Titled “Method for stimulating the intestinal flora”
- Assignee: N. V. Nutricia (Zoetermeer, NL)
- Claim of interest: A method for feeding an infant delivered via caesarean section, comprising: (i) identifying an infant delivered via caesarean section; and (ii) enterally administering to the infant starting within 100 hours after birth a composition comprising: (a) between  $10^3$  and  $10^{13}$  colony forming units (cfu) *Bifidobacterium* consisting of *Bifidobacterium breve*; and (b) between 0.1 and 5 grams indigestible galacto-oligosaccharides per serving.

This claim again illustrates the approach of claiming the administration of a probiotic with a prebiotic that supports the growth or establishment of that probiotic—a so-called “synbiotic.” This claim issued over an obviousness rejection on the basis that while the administration of *B. breve* and indigestible galacto-oligosaccharides to infants was known, the rapid establishment of *B. breve* in infants delivered by C-section to levels similar to those seen in vaginally delivered infants was not expected.

### **U.S. Patent 9,585,416**

- Issued March 7, 2017
- Titled “Preventing diseases in infants delivered via caesarean section”
- Assignee: N.V. Nutricia (Zoetermeer, NL)
- Claim of Interest: **A method for stimulating the development of a healthy intestinal flora and/or decreasing the occurrence of intestinal pathogens in infants delivered via caesarean section comprising administering within 3 months of birth to the infant delivered via caesarean section a composition that is not human milk and comprises: (a) 0.5 to 75 g of non-digestible oligosaccharides per 100 g dry weight of the composition, wherein the non-digestible oligosaccharides comprise galacto-oligosaccharides having at least 50% of its saccharide units of the galacto-oligosaccharides as galactose units, and (b) at least one *Bifidobacterium* selected from the group consisting of *B. longum*, *B. breve*, *B. infantis*, *B. catenulatum*, *B. pseudocatenulatum*, *B. adolescentis*, *B. animalis*, *B. gallicum*, *B. lactis* and *B. bifidum*.**

Another synbiotic example. This patent also issued over an obviousness rejection using the same arguments of unexpected results in infants delivered by C-section relative to those delivered vaginally.

In summary, while these patents each encountered different issues during examination, we’re seeing that examiners are willing to grant broad claims when the specification includes large amounts of supporting data. Demonstrations of synergy or surprising results carry significant weight in overcoming prior art issues, and somewhat surprisingly for this arena, patent-eligible subject matter under 35 U.S.C. §101 is not presenting a major impediment to meaningful claims coverage.

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