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Gut check: microbiome patent update

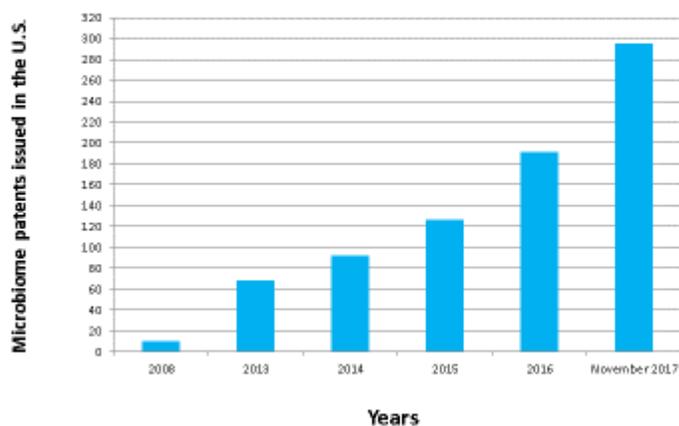
By Mark J. FitzGerald and David S. Resnick

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Recently Issued Microbiome-Related Patents:

U.S. patents in the microbiome space



Over 290 microbiome-related patents have issued in 2017. The examples of recently issued claims in the following are highlighted for their coverage of interesting approaches to securing meaningful patent coverage, and for emphasizing how new trends in the technology are nearly always closely followed by patents covering the subject matter of the trends.

U.S. Patent 9,796,762

- Issued: October 24, 2017
- Titled: “Polypeptide and immune modulation”
- Assignee: 4D Pharma Research Limited (GB)

Claim of interest:

- 1. A method of treating a gastrointestinal inflammatory disorder or an autoimmune disorder, comprising administering to a subject in need thereof a Roseburia flagellin, wherein said Roseburia flagellin is a FlaA1 polypeptide with a sequence that has at least 95% identity to SEQ ID NO:2 or a fragment thereof, and wherein said Roseburia flagellin comprises amino acids 79-117 of SEQ ID NO:2 and binds to TLR5.

This claim is of interest in that it covers a method of treatment based upon the identification of a structural constituent of the subject microbes, as opposed to a microbial metabolite, that influences host immune function. The claim defines the subject flagellin polypeptide by percent sequence identity to a specific reference amino acid sequence, but only requires the administered polypeptide to have 38 amino acids of a much larger reference polypeptide and be able to bind the host toll-like receptor 5 polypeptide. The claims are supported by a highly detailed specification.

U.S. Patent 9,782,431

- Issued: October 10, 2017
- Titled: “Method to prepare hirsutella sinensis polysaccharides possessing anti-obesity properties and uses thereof”
- Assignee: Chang Gung Biotechnology Corp. (Taipei, TW)

Claims of interest:

- 1. A method for treating obesity, comprising administering an effective amount of a polysaccharide extracted from Hirsutella sinensis to a subject in need thereof, wherein the polysaccharide is isolated from a water extract of H. sinensis mycelium and contains at least mannose, glucose, and galactose; wherein treating obesity consists of reducing body weight, body weight gain and fat accumulation.
- 2. The method according to claim 1, wherein the polysaccharide further contains fucose, rhamnose, arabinose, glucosamine and galactosamine.
- 3. The method according to claim 2, wherein a weight ratio of the fucose, rhamnose, arabinose, glucosamine, galactose, glucose, mannose and galactosamine in the polysaccharide ranges from 3:3:1:4:23:12:50:0.2 to 4:4:2:5:24:13:51:0.6.

These claims, like those of the previous patent, are of interest for covering methods of treatment that use not a live microbe or a metabolite of the live microbe, but instead a component of the microbe itself as the therapeutic agent—in this instance, a polysaccharide extract. The component is described, at least in part, in terms of how it is isolated, i.e., a product-by-process, that need not describe the exact components of the composition. However, claim 1 does require the presence of

“at least mannose, glucose and galactose.” Dependent claim 2 adds further saccharide components, and dependent claim 3 adds specific weight ratios of the components recited in claims 2 and 3.

U.S. Patent 9,814,756

- Issued: November 14, 2017
- Titled: “Use of isolated bacterial amyloids for treatment of inflammatory disorders or diseases of the epithelium”
- Assignee: TEMPLE UNIVERSITY (Philadelphia, PA)

Claims of interest:

- 1. A method for the treatment of a subject having inflammatory bowel disease or oral ulcers comprising the step of administering to the subject an effective amount of a composition comprising:
 - a) an isolated curli fibril comprising a naturally occurring CsgA polypeptide, a naturally occurring CsgB polypeptide or a combination of a naturally occurring CsgA polypeptide and a naturally occurring CsgB polypeptide; or
 - b) an isolated curli fibril having epithelium permeability-reducing activity comprising:
 - i. a CsgA polypeptide variant that differs from a naturally occurring CsgA polypeptide in that from 1 to 5 amino acids have been substituted, deleted or added;
 - ii. (ii) a CsgB polypeptide variant that differs from a naturally occurring CsgB polypeptide in that from 1 to 5 amino acids have been substituted, deleted or added; or
 - iii. (iii) a combination of said CsgA polypeptide variant and said CsgB polypeptide variant.
- 9. A method for decreasing permeability of epithelium of the small intestine or large intestine in a subject in need thereof comprising the step of administering to the subject an effective amount of a composition comprising: {same options as claim 1}.

These claims, like those of the preceding two patents, are drawn to methods of treatment using not a live microbe or a metabolite produced by a microbe, but a component of the microbe itself for the treatment of disease. Methods claims of this kind can provide coverage surrounding the discovery of therapeutic properties of such components. A continuation of this method application was filed just before issue of the ‘756 patent—its claims are not publicly available yet, but it would be reasonable to seek protection for compositions comprising the subject polypeptides. § 101 might preclude claiming the polypeptides themselves, but formulations or pharmaceutical compositions including them may well be patent-eligible.

U.S. Patent 9,801,915

- Issued: October 31, 2017
- Titled: “Probiotic and polyphenol against neurodegeneration”
- Assignee: Nestec S.A. (Vevey, CH)

Claim of interest:

- 1. A method of treatment comprising the step of administering a composition comprising *Lactobacillus johnsonii* CNCM 1-1225 in combination with a polyphenol to an individual in need of treatment of a cognitive and/or neurodegenerative disorder selected from the group consisting of Creutzfeldt-Jakob disease and Huntington's disease.

This claim is of interest in that it covers a method of treating the neurodegenerative diseases Huntington's disease or Creutzfeldt-Jakob disease, by administering the specified bacterial strain with a polyphenol. While the strain is specific, the polyphenol is generic. The specification describes a number of specific polyphenols, and the dependent claims recite rosmarinic acid, chicoric acid, caftaric acid and combinations thereof. The claim is also interesting from a scientific standpoint, in that both Creutzfeldt-Jakob and Huntington's diseases involve inappropriate protein aggregation. The claims are supported by two in vitro assays that examine the effect of the recited combination of *L. johnsonii* CNCM 1-1225 with various polyphenols on aggregation behavior of amyloid beta ($A\beta$ -42), a reminder that appropriate in vitro assays can support method of treatment claims.

U.S. Patent 9,816,150

- Issued: November 14, 2017
- Titled: "Method for selection of agents influencing intestinal motility disorders and pain"
- Assignee: BioGaia AB (Stockholm, SE)

Claims of interest:

- 1. A bacterial strain that increases migrating motor complex (MMC) frequency, MMC velocity and intraluminal peak pressure and decreases mesenteric afferent nerve firing, wherein the bacterial strain is *Lactobacillus gasseri* 345A (LG345A) having been deposited under DSMZ Accession No. DSM 27123.
- 2. A bacterial strain that decreases MMC velocity and decreases mesenteric afferent nerve firing, wherein the bacterial strain is *Lactobacillus gasseri* 621A (LG621A) having been deposited under DSMZ Accession No. DSM-27126.
- 9. A composition comprising the bacterial strain of claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.
- 10. A composition comprising the bacterial strain of claim 1 and a foodstuff or food supplement.
- 12. A composition comprising the bacterial strain of claim 2 and a pharmaceutically acceptable carrier, diluent or excipient.
- 13. A composition comprising the bacterial strain of claim 2 and a foodstuff or food supplement.

These claims are of interest in being drawn to specific strains of *L. gasseri* that modulate gut motility and pain signaling. A related application resulted in the grant of claims (U.S. 9,555,065) in January 2017 to methods of treating an intestinal motility disorder by administering a probiotic strain. In the independent claims of the '065 patent, the strain is defined only by its method of selection; dependent claims in the '065 patent identify the strains recited in the claims of the '150 patent that issued in November. This is yet another example of a broad composition claim issuing after the Applicant initially pursued methods claims that use newly identified microbial strains.

The file history was brief, and there was no § 101 issue raised over any of the claims. It is noted that dependent composition claims for each of claims 1 and 2 recite pharmaceutical compositions and compositions comprising a foodstuff or food supplement comprising the subject strains. The recitation of a pharmaceutical composition or a composition that includes a foodstuff likely assists in distinguishing a naturally occurring composition.

U.S. Patent 9,805,171

- Issued: October 31, 2017
- Titled: “Modifying a cosmetic product based on a microbe profile”
- Assignee: Elwha LLC (Bellevue, WA)

Claim of interest:

- 1. A system for modifying a cosmetic product, comprising: an ingredient-microbe interaction dataset including information associated with chemical interactions between one or more reference cosmetic ingredients and one or more types of reference microbes, wherein said chemical interactions alter at least one of a color, a texture or an odor of the one or more reference cosmetic ingredients; and a computing device including a processor and circuitry, the circuitry configured to receive information associated with a microbe profile of an individual, the microbe profile including a distribution and identity of one or more types of microbes on a skin surface of the individual; receive information associated with an ingredient list of the cosmetic product, the ingredient list including one or more cosmetic ingredients; compare the ingredient-microbe interaction dataset to the received information associated with the microbe profile of the individual and the received information associated with the ingredient list of the cosmetic product; identify a chemical interaction between at least one of the one or more cosmetic ingredients in the ingredient list of the cosmetic product and at least one of the one or more types of microbes in the microbe profile of the individual based on the comparison with the ingredient-microbe interaction dataset, wherein the identified chemical interaction alters at least one of the color, the texture or the odor of the at least one of the one or more cosmetic ingredients; recommend a modification to the ingredient list of the cosmetic product in response to the identified chemical interaction between the at least one of the one or more cosmetic ingredients in the ingredient list of the cosmetic product and the at least one of the one or more types of microbes in the microbe profile of the individual; and report to a user the recommended modification to the ingredient list of the cosmetic product.

This claim is of interest in being directed to a system (as opposed to a method) for modifying a cosmetic product. The system uses information regarding the interactions between reference microbes and chemical ingredients of cosmetic products. The system will recommend a modification to the ingredients of a cosmetic product based on the skin microbiome profile of an individual, to impact the color, texture or odor of a cosmetic ingredient.

The system claim is also of interest in that it does not require an actual modification be made to a subject cosmetic. Rather, the system, which requires a computing device including a processor and circuitry, will recommend a modification and report that modification to a user. The Applicants did not encounter § 101 patent-eligible subject matter issues during examination.

Comments/Conclusions:

It is by now common to see claims that recite particular microbial isolates, whether naturally occurring or genetically modified, and to see claims that refer to the products produced by these or other microbes. Three recent examples discussed herein show a trend toward claims that recite components of the microbes themselves, rather than the microbes or their metabolites. While the claims of this kind noted herein are drawn to methods of treatment, it should be possible, as such components are identified, to obtain composition claim coverage drawn to pharmaceutical formulations including such components.

Similarly, composition claims drawn to microbes in pharmaceutical formulations or in compositions including foodstuffs provide avenues for composition protection surrounding microbial isolates.

Finally, claims discussed herein also reinforce the ability to obtain method of treatment claims supported by in vitro assays that are reasonably predictive of in vivo outcome.

Answers to Questions from our Microbiome IP Webinar:

The following provides some more detail around the various questions submitted during the [November 7 webinar](#) “Gut Check: Scoping out Patents and the Microbiome.”

How is claiming OTU % identity not the same thing as claiming a naturally occurring microorganism?

The OTU approach is a way of defining the subject microorganism in a way that the Patent Office has viewed as satisfying the definiteness requirement under 35 U.S.C. §112(b). Reciting OTU % identity describes the subject microorganism, whether in the context of a composition claim or a method claim, more broadly than recitation of a particular microbial genus and species alone. A claim that defines the subject microorganism in this manner will cover a composition or use that involves any microorganism in which the reference sequence, e.g., 16S rDNA sequence, has the recited degree of identity. Defining the subject microorganisms in this way does not address the § 101 patent-eligible subject matter issue of claiming a naturally occurring microorganism itself—that issue needs to be addressed by claiming a formulation that includes more than the naturally occurring microorganism itself, or by claiming a method of using the microorganism.

I’m still confused about how many of these claims are not simply claiming the natural ability of an organism or just a naturally occurring organism. Can you clarify how you walk that thin line?

Under § 101, while a natural phenomenon, e.g., the ability of a microbe to generate a given metabolite, is not patent-eligible, applications of that phenomenon are. Thus, a claim reciting a method of treating a disease by administering a microorganism that generates the given metabolite is a specific application of the phenomenon, and generally patent-eligible.

Composition claims are a bit trickier, because the microorganism itself is not patent-eligible. This is where formulations come in that require more than the microorganism itself, e.g., the microorganism in an enteric delivery form, in combination with a foodstuff or a prebiotic, or as a

particular proportion of the biomass of a composition. As the various claims noted in the webinar show, the Patent Office is not always consistent in applying the standard to compositions including microorganisms, with some examiners accepting, for example the requirement that the microorganism preparation be simply “biologically pure,” and others requiring, for example, recitation of specific proportions of specific ingredients other than the microorganism. In our view, it is best to describe the microorganism and various formulations in the specification in as many different ways as possible, and to pursue composition claims with varying degrees of detail. If we are able to get claims drawn to a minimal composition, we generally don’t rest on these, but pursue further claims, e.g., in one or more continuation applications, that describe formulations including the microorganism in more detail. In this way, if the validity of an issued claim that recites a minimal composition is successfully challenged, there can be other composition claims that stand.

And finally, as noted in the webinar, there can be valid composition claims drawn to a consortium of microorganisms if the members of the consortium act synergistically in some meaningful manner. The mixture of microorganisms does something together that the microorganisms do not do separately. You are not patenting the microorganisms themselves, but rather the specific mixture of them.

Given the difficulty in getting “prevention” claims, what do you recommend for claims or specification support for technologies that use microbes prophylactically?

The ability to get claims drawn to “prevention” for any type of agent depends on presenting data showing such prevention, so it really comes down to the strength of your animal model(s). For example, where there can be many different causes of a given condition, e.g., hypertension or cancer, it will be difficult to obtain coverage for prevention of those conditions absent a demonstration that a given treatment prevents the condition as caused by different things. That said, if a given agent can be shown in an animal model to prevent, e.g., hypertension caused by a given factor, one may be able to get “prevention” type claims if the disorder to be prevented is limited in the claims to hypertension caused by that factor, rather than hypertension generally. The microbiome-related prevention claims noted in the webinar benefitted from the strength of the model systems available.

In our view, it is best for the specification to provide real data, in at least one animal model, that demonstrates prevention. That is, the animal given the microbes before challenge with a disease-causing agent, e.g., a pathogenic microbe, does not develop the pathology that an animal not given the microbes does.

Do you think the USPTO and EPO will continue to allow broad claims on very vague information? Or will they crack down. Have there been any significant private challenges to these patents?

We expect the allowable scope of the claims to evolve over time, much like the scope of antibody claims has evolved. Probably the biggest driver of this will be ongoing discovery in this space, such that the prior art gets both deeper and broader—applicants will have to describe the microorganisms and what they do more narrowly as time goes on in order to avoid encompassing the prior art, whether by lacking novelty or being obvious over such prior art. By analogy, where one could once obtain claims to simply a monoclonal antibody that binds a given known antigen, today, because it is viewed as routine and therefore obvious to raise monoclonal antibodies to almost any antigen, it is most often necessary to limit antibody composition claims to recite

specific CDR sequences. In this manner, the breadth seen today is likely to be limited over time without an actual crack down by the patent offices.

Of course, if there are high profile challenges to the validity of broad claims in this area, the patent offices may also take a harder line. We are not aware of any such challenges to date, but as these patents begin to be enforced against accused infringers, validity challenges are inevitable.

In the example of the Whole Biome patent, you mentioned that you need to be careful with the breadth of how you define a microorganism, as that could include a pathogen. From purely a standpoint of protecting yourself as much as possible, why is that a bad thing? Does having a pathogen within a claim gate affect the examination by the PTO (of course the pathogen would not go into the eventual product)?

This is a good question. At one level, the easy answer is that if the description of the microorganisms in a claim encompasses a pathogen, either the patent examiner or an accused infringer can argue that the claim is invalid for lack of enablement over its full scope. That is, the claimed method or composition will not work for the given therapeutic or prophylactic purpose if it makes the subject sick. However, under the law of enablement, claims are permitted to encompass some degree of non-functional embodiments, if the majority of embodiments encompassed are functional and one of skill in the art would readily recognize those that are not.

What is important in this context, in our view, is to be careful in defining the microorganisms encompassed, and at least be aware of scope that encompasses a pathogen or other microorganisms known not to be functional. If you're aware of it, you can avoid a protracted enablement battle with the Patent Office or nasty surprises down the road during enforcement, and you can also add description to the specification that will permit you to include a negative limitation in the claims to exclude the pathogenic or otherwise non-functional organisms if you have to.

As a genomic scientist, I know the composition of bacteria mixture can be determined and quantified—Why didn't the applications try to include this?

It does make sense that if the technology permits a determination of the various species in a mixture and their relative proportions, this information can be helpful to support patent claims. However, a claim that describes the identity of every microorganism in a complex mixture will be narrowly construed to include all of those microorganisms. This provides some level of protection, but infringement is easily avoided by leaving one of the recited microorganisms out. If you know which organisms are necessary for the effect observed, or what they're actually doing that contributes to the effect, you can avoid that scenario by reciting only those members of a mixture that are necessary in the claims.

Including definition of organisms by deposit still seems to be an important fall-back position. Many applicants do not like the possibility of having to make these deposits available, particularly if claims have to be restricted so as not to cover some of the deposits provided in the application. When are these deposits available to third parties in the U.S. and are there any strategies for limiting this?

Deposited strains do become available when the patent issues. If the claims that issue do not cover the deposited strains or their use, it is advisable to pursue such claims in a continuation, or where the claims were not examined due to a Restriction Requirement, in one or more divisional applications. Pending claims that may issue can be a reasonably strong deterrent for third parties to

invest heavily in uses of those strains. Some still swear by keeping at least one application pending in any commercially important patent family, to maintain an ability to tailor claims to cover competitors' products as they emerge; keeping competitors on guard for the potential issue of claims covering deposited strains is another good reason to do so.

Of course, the best way to avoid having deposited strains become available as soon as the patent issues is to avoid deposit where at all possible. However, for commercially relevant strains, this may not be possible where there is no other way to describe a microbe that does exactly what your isolated strain does. For example, if you don't know what product(s) or pathways active in the microbe are responsible for the activity in which you are interested, deposit may be the only viable option.

How about the process of working with the FDA to get a new microbe approved for human use?

This is a good question, but beyond the scope of material for which the Patent Office has authority, and beyond the scope of our topic. Regulatory standards in this area are evolving. Where a microorganism is isolated from, e.g., the healthy human gut, it can fall into the category of those generally recognized as safe (GRAS) and potentially face an easier road to approval. Modified microbes and microbes isolated from other sources would likely face added scrutiny.

Is there any kind of re-examination (post grant review, etc.) ongoing on the issued patents related to the microbiome?

While we have not exhaustively searched, we have not seen any. However, as these patents are enforced against accused infringers, that will almost definitely change.

Some upcoming microbiome-related conferences/webinars:

Microbiome Drug Development Europe, January 29–February 1, 2018, Paris, France.

<http://microbiome-europe.com/> **Mark FitzGerald (Nixon Peabody LLP) will be attending.**

3rd Annual North American Microbiome Congress, February 5–7, San Diego, CA.

<https://humanmicrobiomecongress.com/events/north-america-microbiome-congress>

Microbiome-Based Precision Medicine, February 15–16, San Francisco, CA.

<http://www.triconference.com/Microbiome/>

Microbiome AgBio Tech Summit, February 27–28, Raleigh, NC.

<http://microbiome-agbiotech.com/>

Microbiome Data to Knowledge, March 16, Seattle, WA.

<https://www.fredhutch.org/en/labs/phs/projects/biostats/events/microbiome2018.html>

4th Annual Translational Microbiome Conference, April 18–20, Boston, MA

<http://www.microbiomeconference.com/> **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.**

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