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Gut check: microbiome patent update

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In this issue:

- Trends in microbiome-related investment
- A new approach to address the critical need for computing power in microbiome data crunching
- Analysis of recently issued microbiome-related patent claims
- Some upcoming microbiome-related webinars and conferences

Trends in microbiome-related investment

We've all seen interest in microbiome-related technology surge in recent years. A new report from SVB Analytics titled "Emerging Healthcare: Microbiome Investment Trends" nicely sums up the current state of things. A few key points:

- There has been $840 M invested in 45 disclosed equity investments since 2010, and investment levels are on course to set a new record in 2017.
- Almost half of all investment is in companies focused on gastrointestinal disorders and infectious disease, but cancer, autoimmune disease, dermatology and disorders of the central nervous system are also attracting significant investment.
- The investment landscape is highly fragmented: 87% of microbiome investors have made only one investment in the subsector, but several major players have emerged:
    a) Johnson & Johnson, through the Janssen Human Microbiome Institute
    b) Seventure Partners, based in France, has a $175+M fund dedicated to microbiome investments
    c) Illumina—logical, given the key role genomic sequencing and bioinformatics has played and will play going forward.

The full report is available here.

Data crunching for microbiome research

One of the most critical needs in translating microbiome research into therapeutic and commercial successes is management and analysis of the massive amount of data related to the various "-omes" involved—genomes, transcriptomes, metabolomes, among others. This takes massive amounts of computing power. A new approach, possibly inspired by that used in the search for extraterrestrial intelligence (e.g., the SETI Institute), crowd sources computing power, and YOU can help!

IBM, the Broad Institute and Massachusetts General Hospital have launched a crowdsourced human microbiome computation project in which anyone can contribute unused computational time to help. Using IBM's World Community Grid, the goal is to get computer users from all over the globe to donate computational power to the effort. Computer users can download a secure software program that automatically detects when a computer has unused processing power, and uses it to run analyses for the Microbiome Immunity Project. More details are here and here.

Recently issued microbiome-related patents

U.S. patents directed to microbiome-related technologies are being applied for and issuing at the fastest rate ever. The examples of recently issued claims in the following are highlighted for their coverage of interesting science and for notable prosecution devices or approaches to secure that coverage.

U.S. Patent 9,706,778

- Issued: July 18, 2017
- Titled: "Materials and methods for improving immune responses and skin and/or mucosal barrier functions"
- Assignee: Quorum Innovations, LLC (Sarasota, FL)

Claims of interest:

- 1. A method for inhibiting microbial growth on a surface, wherein the method comprises applying to the surface a microbial growth-inhibiting amount of a composition comprising a bioactive *Lactobacillus fermentum* strain having an Accession No. PTA-122195 grown as a biofilm.
- 2. The method, according to claim 1, wherein the surface is skin.
- 3. The method, according to claim 2, wherein skin barrier function is enhanced.
- 6. The method, according to claim 1, wherein the method promotes the growth of commensal bacteria.
- 9. The method, according to claim 1, wherein the method inhibits the growth of methicillin-resistant *Staphylococcus aureus* (MRSA).

These claims are of interest for covering the use of a *Lactobacillus* strain grown as a biofilm to inhibit microbial growth on a surface, including the skin. Biofilm formation by pathogenic bacteria contributes to antibiotic resistance—it's interesting from a scientific standpoint to use bacteria grown as a biofilm to inhibit the growth of biofilm-forming pathogens.

The dependent claims indicate that the biofilm-produced composition promotes the growth of commensal bacteria and inhibits the growth of pathogenic bacteria, including MRSA. This activity is supported by working examples in the specification demonstrating that the specified strain has both activities.

The applicants overcame enablement and prior art rejections by amendment to recite the specified strain, which was deposited under the Budapest Treaty.

The applicants obtained accelerated examination under a Petition to Make Special based on applicant's age, rather than using the Track One procedure—this route is available if any applicant is over 65 years of age.

U.S. Patent 9,701,964

- Issued: July 11, 2017
- Titled: "Altering microbial populations and modifying microbiota"
- Assignee: SNIPR Technologies Limited (London, GB)

Claims of interest:

- 1. A method of modifying a mixed population of microbiota bacteria, the mixed population comprising a first and a second bacterial sub-population wherein the first sub-population comprises a first microbiota species and the second sub-population comprises a host cell population of a second microbiota species, wherein the second species is a different species than the first microbiota species and bacteria of said second species comprise endogenous nucleic acid encoding a functional endogenous Cas nuclease, the method comprising
    a) a. combining the mixed population of microbiota bacteria with multiple copies of engineered nucleic acid sequences encoding host modifying (HM) crRNAs, and
    b) b. expressing HM-crRNAs in host cells, wherein each HM-crRNA is encoded by a respective engineered nucleic acid sequence and is operable with the functional expressed endogenous Cas nuclease endogenous to said second species of bacteria and expressed in a respective host cell,

    said expressed endogenous Cas nuclease being active in said respective host cell, wherein said respective engineered nucleic acid sequence and Cas form a HM-CRISPR/Cas system and the engineered nucleic acid sequence comprises

        i. a nucleic acid sequence comprising spacer and repeat sequences encoding said HM-crRNA;
        ii. a nucleic acid sequence encoding a sequence of said HM-crRNA, wherein said HM-crRNA sequence is capable of hybridizing to a host cell target sequence to guide endogenous Cas nuclease to the target sequence in the host cell;

    and wherein the engineered nucleic acid sequence does not encode said Cas nuclease that is endogenous to said second species of bacteria;

    and optionally the HM-system comprises a tracrRNA sequence or a DNA sequence expressing a tracrRNA sequence;

    whereby HM-crRNAs guide endogenous Cas activity to modify host target sequences in host cells, whereby host cells are killed or the host cell population growth is reduced, thereby reducing the proportion of said host cell population and altering the relative ratio of said sub-populations of bacteria in the mixed bacterial population.
- 15. The method of claim 1 for treating a host cell infection of a human or animal subject,

the method comprising exposing the host cells to a first antibiotic simultaneously or sequentially with said engineered nucleic acid sequences encoding HM-crRNAs, wherein target sequences are each comprised by an antibiotic resistance gene for resistance to said first antibiotic, wherein the host cell infection is treated in the subject.

Many therapeutic approaches aim to out-compete or replace undesirable microbiota bacteria with probiotic species, sometimes in combination with broad-spectrum antibiotics to pave the way. In contrast, this patent covers a targeted method of killing or reducing growth of a population of microbiota bacteria using CRISPR and harnessing endogenous Cas endonuclease activity in the target microbes to do it.

The noted dependent claim combines the targeting of an antibiotic resistance gene with the administration of an antibiotic, which would overcome the resistance problem.

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

U.S. Patent 9,737,575

- Issued: August 22, 2017
- Titled: "Use of lactic acid bacteria to treat or prevent eczema"
- Assignee: University of Otago (Dunedin, NZ)

Claims of interest:

- 1. A method of treating or preventing eczema in a subject, the method comprising oral administration of an effective amount of the viable *Lactobacillus rhamnosus* HN001, AGAL deposit number NM97/09514 dated 18 Aug. 1997, to a subject in need thereof.
- 6. The method of claim 1 wherein the method is a method of preventing eczema.
- 11. The method of claim 1, wherein the viable Lactobacillus rhamnosus HN001 is administered separately, simultaneously or sequentially with one or more agents selected from one or more probioitics, one or more prebiotics, one or more sources of dietary fibre, one or more galactooligosaccharides, one or more short-chain galactooligosaccharides, one or more long-chain galactooligosaccharides, one or more fructooligosaccharides, one or more short-chain galactooligosaccharides, one or more long-chain galactooligosaccharides, inulin, one or more galactans, one or more fructans, lactulose or any mixture of any two or more thereof.

These claims are of interest for covering a method of not only treating, but *preventing* eczema in a subject by administering a specified strain of *L. rhamnosus*. It is often difficult to get explicit coverage for prevention in other areas of medicine, but we are seeing a reasonable number of claims issue in the microbiome arena that recite prevention. Such claims nearly always require working examples in at least an animal model to show efficacy, and this patent is no exception—prevention is supported in the Examples by double-blind, placebo-controlled human clinical studies of pregnant mothers and their infants through two years postpartum.

The claims are limited to the specific deposited strain, applicants having overcome an obviousness rejection over another strain of *L. rhamnosus* on the basis of superior efficacy/surprising results.

U.S. Patent 9,738,870

- Issued: August 22, 2017
- Titled: “Ammonia oxidizing bacteria for treatment of acne”
- Assignee: AOBiome LLC (Cambridge, MA)

Claims of interest:

- 1. A method of treating an inflammatory lesion or a non-inflammatory lesion of acne in a subject, comprising: administering, as a spray, aerosol or mist, a preparation comprising live ammonia oxidizing bacteria, to the skin of the subject, in an amount effective to treat an inflammatory lesion or a non-inflammatory lesion of acne.
- 11. The method of claim 1, wherein the ammonia oxidizing bacteria is selected from the group consisting of *Nitrosomonas, Nitrosococcus, Nitrosospira, Nitrosocystis, Nitrosolobus, Nitrosovibrio* and combinations thereof.
- 12. The method of claim 11, wherein the ammonia oxidizing bacteria is *Nitrosomonas eutropha* (*N. eutropha*).
- 13. The method of claim 12, wherein the ammonia oxidizing bacteria is *N. eutropha* D23, having ATCC accession number PTA-121157.

These method claims are of interest because the independent claim characterizes the subject microbes by function alone, rather than by species or strain of ammonia oxidizing bacteria. The specification is detailed, includes a lengthy Sequence Listing and describes successful placebo-controlled human clinical trials.

While not prosecuted under the Track One accelerated examination procedure, the pendency of this application was under two years and involved only one Office Action. After responding to the Office Action, the applicants conducted an in-person examiner interview that included an inventor. Allowance followed shortly thereafter.

U.S. Patent 9,730,969

- Issued: August 15, 2017
- Titled: “Nutritional compositions for promoting gut barrier function and ameliorating visceral pain”
- Assignee: Mead Johnson Nutrition Company (Glenview, IL)

Claims of interest:

1. A method for i) promoting gut barrier regeneration, ii) promoting gut barrier maturation and/or adaptation, iii) supporting gut barrier resistance and/or iv) protecting gut barrier function in a pediatric subject in need thereof, comprising:

administering to the pediatric subject a composition comprising an effective amount of a soluble mediator preparation from a late-exponential growth phase of a *Lactobacillus rhamnosus* GG (LGG) batch-cultivation process, wherein the soluble mediator preparation is produced by

a) subjecting LGG to cultivation in a suitable medium using a batch process;
b) harvesting a culture supernatant at a late exponential growth phase of the cultivation step, which phase is defined with reference to the second half of the

time between the lag phase and the stationary phase of the batch-cultivation process;

c) optionally removing low molecular weight constituents from the supernatant so as to retain molecular weight constituents above 5 or 6 kDa;
d) removing any remaining cells by 0.2 μm sterile filtration to provide the soluble mediator preparation;
e) removing liquid contents from the soluble mediator preparation so as to obtain the composition.

This claim is of interest as a method of treatment of any of the noted pediatric gut barrier issues, involving administration of a composition prepared from a culture of a specific strain of *Lactobacillus* bacterium in the late exponential growth phase—that is, a method of treatment with a composition defined as a product-by-process. Some look down upon product-by-process claims, but they serve a purpose where, as here, the exact make-up of the subject composition (culture medium from late-exponential phase growth of *L. rhamnosus* GG) is not necessarily known, but is defined by the described conditions of culture. In this method of treatment claim, as opposed to a composition claim, the product-by-process language need not necessarily define a composition that distinguishes the prior art. The applicants overcame an obviousness rejection by requiring the removal of *all* cells from the preparation.

Some upcoming microbiome-related conferences/webinars:

Gut Check: Expanding Your Scope —Patents and the Microbiome

The Microbiome Coalition, Nixon Peabody LLP and Icosa are co-hosting a webinar "Gut Check: Expanding Your Scope—Patents and the Microbiome" on November 7, 2017 from 12:30 to 2:00 p.m. Eastern time. Nixon Peabody patent attorneys Mark FitzGerald and David Resnick will present on strategies for patent protection in the U.S., and Icosa European patent attorney Caroline de Mareuil-Villette will present a European perspective. For more information, please contact Kristen DeCandia at kdecandia@nixonpeabody.com.

Microbiome R&D Business Collaboration Forum and 2nd Probiotics Congress

A merger of the Global Engage 5th Microbiome R&D Business Collaboration Forum USA with the 2nd Probiotics Congress USA is set for November 2 and 3 in San Diego, CA. More information is available here.

Microbiome in Human Nutrition conference

Microbiome in Human Nutrition conference, November 14–16, Boston, MA. Speakers include Professor Rob Knight of UCSD, and representatives of Nestle Health Science, Danone Nutricia, Mead Johnson Nutrition, USDA and the Bill & Melinda Gates Foundation, among others. More information is available here:

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