DEEP DIVE: MICROBIOME 2016
Beyond Digestion, the Human Ecosystem

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INTRODUCTION

It takes a village

Ayn Rand got it wrong. It turns out that the idea of the rugged individual standing apart from the crowd, ruled solely by his own reason is a romantic one—at least as far as human health is concerned.

We are not alone in our bodies. We share this flesh with a mind-boggling number of microorganisms. These microbes largely consist of bacteria but also include a menagerie of other microscopic critters and particles such as eukaryotes, archaea and viruses. The totality is known as the microbiome, a community of up to 100 trillion cells that represent 99 percent of the genetic material in the human body.

If the idea that we are genetically more bacteria than human is a disturbing one—we still outweigh our microbiome by up to 99 percent based on mass—then take solace in the fact that these microbes are mostly benign. In fact, they are essential for maintaining health, according to the Human Microbiome Project (HMP), a National Institutes of Health-funded initiative started in 2008 to help characterize the human microbiome and understand its role in human health and disease.

Human microbes do almost everything but the dishes. They produce some vitamins that we can’t make ourselves, help us extract nutrients from food, and play important roles in our immune system and inflammatory responses. A preponderance of research suggests that changes in the microbiome are closely related to numerous diseases, hinting at a new target for treating and preventing illness.

In other words, it takes a village—well, a megalopolis—to help the human body function well. Ingredient manufacturers are already moving into this brave new world with products that may boost the bugs that help us survive and thrive.
“After decades in the field and only being able to treat symptoms, we finally have the ability to possibly get to the root cause of so many of our pernicious maladies.” — Dr. David Perlmutter

Big focus on research

In less than a century, non-communicable diseases have surpassed infectious diseases as the principal cause of sickness and death worldwide. These run the gamut from irritable bowel syndrome to diabetes to Alzheimer’s disease. Study after study shows that a disgruntled microbiome, particularly the community that congregates in the gut, may be at the heart of many of these chronic disease states. It’s no surprise, then, that unlocking the secrets of the microbiome has become the raison d’etre among many researchers in the medical field.

“After decades in the field and only being able to treat symptoms, we finally have the ability to possibly get to the root cause of so many of our pernicious maladies. Examples are diseases such as Parkinson’s, Alzheimer’s, amyotrophic lateral sclerosis (ALS), autism, attention-deficit hyperactivity disorder and depression,” said Dr. David Perlmutter in an interview published in the journal Alternative and Complementary Therapies in June of this year.ii

Perlmutter, of course, has helped popularize the notion that the microbiome is more than just a gut feeling with two best-selling books, linking the health of the brain with the health of the microbiome. The so-called microbiome-gut-brain axis is just one of many areas of study underway in the explosive field of microbiome research.

This report will primarily probe the microbiome and functional ingredients beyond gut health, including the gut-brain axis, immunity, oral health, the skin microbiome, metabolic diseases and others.

Microbiome publications have ballooned from 78 in 2000 to more than 2,000 in 2013.iii A search on “microbiome” on PubMed returns about 25,000 hits, with nearly 500 projects on ClinicalTrials.gov. The Obama administration in May of this year answered the call of researchers for more funding, with the National Microbiome Initiative. The government will invest $121 million over the next two years in research spanning the microbial health of the planet.
Concurrently, more than 100 other institutions announced their intentions to support microbiome science, including $100 million from the Bill and Melinda Gates Foundation. iv The Mayo Clinic Center for Individualized Medicine committed to establishing a Microbiome Clinic, offering clinical services, diagnostics and patient education as part of its Microbiome Program. In addition, the nonprofit medical treatment and research institution has entered into a number of collaborations with startups, such as Evelo Biosciences, which is developing cancer-associated bacteria as a possible therapy based on their ability to activate the immune system against tumors.

Global biosciences company Chr. Hansen is also betting on the microbiome in a big way. Last year, the Denmark-based company announced its intention to partner with three academic institutions working in the field of anaerobic bacteria and host-microbe interactions. The consortium will operate a research program aimed at exploiting the human microbiome and developing bacterial products that can improve human health, such as preventing and treating gastrointestinal and metabolic diseases, according to a company press release.v

“‐The microbiome is a very hot topic, but it is also a nebulous concept to most consumers,” conceded Mike Bush, president of probiotics manufacturer Ganeden Biotech and executive board president of the International Probiotics Association (IPA). Ganeden’s flagship product is GanedenBC30 (Bacillus coagulans), which can be found in more than 50 foods. “We are currently involved in a variety of microbiome‐related work, and our goal at Ganeden is to continue being at the forefront of probiotic research and product development.”

In an interview with NPR’s Terry Gross this summer, science journalist Ed Yong discussed his new book, I Contain Multitudes: The Microbes Within Us and a Grander View of Life. He told Gross that he is cautiously optimistic about the future of microbial research and its potential to improve human health.

“I think the potential there is huge because the microbiome is theoretically very flexible,” he said during the radio interview. “We should be able to change it. We just don’t quite know how yet.”

Scientists had been limited in their investigations into the human microbiome because they used culture-based techniques, which rely on cultivating and isolating microorganisms that thrive in standard laboratory conditions, which represents less than 10 percent of human microbiota. The advent of next‐generation sequencing technologies has changed the game. Using DNA sequencing methodology, researchers are now able to characterize and analyze microbiomes with greater precision and accuracy, and with less bias, compared to culture-based approaches.vi
Big business ahead …

Scientists will urge caution before we begin to tinker with treatments targeting the microbiome. Meanwhile, the functional food and ingredient markets will continue to meet consumer demands for gut health—and beyond.

Gastrointestinal health supplements reached sales of $2.1 billion with 11.9 percent growth in 2014, according to data from Nutrition Business Journal’s 2015 Supplement Report. About 5.7 percent of products in the condition-specific supplements category are geared toward this market.

Going beyond GI health where the microbiome may also hold sway—such as brain health, immunity, weight loss, skin health and metabolic-related disorders like diabetes—suggests that the microbiome could be a multibillion business someday if the science makes good on its promise. Consider these numbers from NBJ on condition-specific sales in the following areas from 2014:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sales 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Health</td>
<td>$634MILLION</td>
</tr>
<tr>
<td>Cold/Flu/Immunity</td>
<td>$2.5BILLION</td>
</tr>
<tr>
<td>Sports/Energy/Weight Loss</td>
<td>$10.2MILLION</td>
</tr>
<tr>
<td>Diabetes:</td>
<td>$1.4BILLION</td>
</tr>
<tr>
<td>Hair/SkinNails:</td>
<td>$816BILLION</td>
</tr>
</tbody>
</table>

Some firms are also specifically tracking the microbiome market. Markets and Markets released a report earlier this year that said the human microbiome market is expected to reach $658 million by 2023 from $294 million in 2019, growing at a rate of 22.3 percent during the forecast period.\(^vii\)

Markets and Markets predicts that therapeutics will account for the largest market share in the human microbiome market from 2019 onwards. “Factors such as rising incidences of lifestyle diseases, increasing aging population and technological developments such as microbiome sequencing drive the growth of the human microbiome market,” it reported. “On the basis of disease, the human microbiome market comprises of obesity, diabetes, autoimmune disorder, acute diarrhea, cancer, mental disorder and others. Among these, the acute diarrhea segment is expected to account for the largest share and will be the fastest-growing segment in 2019, followed by obesity.”
The role of probiotics, in particular, in the microbiome revolution can’t be understated. The Markets and Markets report puts it bluntly: “Probiotics is expected to account for the largest market share and will also register a growth rate of 25.2 percent in the forecasted period of 2019 to 2023.”

NBJ pegged sales of probiotic supplements at $1.4 billion in 2014, up 18 percent over 2013. By next year, NBJ predicts sales to grow to $2.1 billion and projects the market to reach $3.1 billion by 2020. The probiotic foods market is even bigger, with sales reaching $7 billion in 2013, according to NBJ, with the market estimated to increase to $10 billion by 2018.

Probiotics are also one of the most successful categories in the global market, though the numbers vary widely depending on who is doing the counting. According to Euromonitor International, global probiotic sales are $35 billion and are expected to reach $48 billion by 2020. Grand View Research put a price tag of about $32 billion on the market in 2013. BCC Research was also in the same price range, valuing the global probiotics market at $34 billion in 2015, and projecting a compound annual growth rate (CAGR) of 8 percent, to bring the market up to an even $50 billion by 2020. Allied Market Research expects the global probiotics market to reach $57.4 billion by 2022, with a CAGR of 7.7 percent during the 2016-2022 forecast period. Others may be especially pleased (or suspicious) with Transparency Market Research, which valued the global probiotic market at $62 billion in 2014, predicting it will near the $100 billion mark by the end of 2020.

Most of these market research companies can agree on a couple of points. One, the Asia-Pacific market dominates; Grand View Research estimates that the region accounted for more than 40 percent of total revenues in 2013, for example. Second, the food and beverage segment continues to be the big money earner, accounting for three-quarters or more of total sales.

... And some big obstacles to overcome

All those dollar signs and double-digit growth predictions come with some sobering realities, particularly for those companies that are bullish on beyond-the-gut health.

The usual regulatory red tape aside—let’s not even discuss the perpetual roadblock known as the European Food Safety Authority—there are plenty of red flags to the microbiome revolution that companies might consider before joining the ranks.

Much of the research—and there is a lot of it, as nary a day goes by without the headline-making release of a new scientific paper on the microbiome—is preliminary and preclinical.
Rob Knight, a leading researcher in the microbiome field from the University of Colorado, told NBJ’s Rick Polito in a previous article: “Much of the basic knowledge we need about which microbial changes will lead to improved health— as opposed to resulting from improved health— has not yet been done.”

If we are talking probiotics—and oftentimes we are when it comes to functional foods and ingredients in relation to the microbiome—then not just any old strain will do, according to Mary Ellen Sanders, a consultant with Colorado-based Dairy & Food Culture Technologies. Microbiota for gut health is one thing, she explained, but to address health conditions in other areas, from diabetes to bad breath requires a different kind of bug.

“Each of those is really going to require a specific strain that’s got those capabilities,” she said. “I don’t think you can go in there with any strain and expect to see results.”

Obviously, the science must be sound, backed up by not just preclinical studies on fat and skinny mice, for example, but robust human trials. “The trials are expensive. They’re difficult to do,” Sanders noted.

And few people are doing human trials on the benefits of probiotics or other ingredients on the body’s microbiome, whether in the gut, the mouth or the skin, aside from the industry itself. And there will always be critics of industry-backed research, regardless of how scrupulous and rigorous the study. [See sidebar/boxed inset.]

“The biggest challenge is education,” said Ganeden’s Bush, whose company’s latest ingredient, Bonicel, is a unique byproduct created during the fermentation of its proprietary probiotic, GanedenBC30. Ganeden touts Bonicel as the first probiotic-derived personal care ingredient. It’s backed by four clinical studies that suggest it can increase skin hydration and elasticity and reduce the appearance of fine lines, wrinkles, roughness, pore size and redness.

“We put great value in only producing ingredients that are science-backed, with credible research supporting the claims,” Bush said. “When considering skincare ingredients, formulators need to look at the clinical studies supporting the exact ingredient, to determine whether or not that ingredient will produce the desired effect in the finished product.”
Nena Dockery, technical services manager at Stratum Nutrition, also hits the education theme hard when discussing her company’s probiotic oral care product, BLIS K12®. The antibiotic and antibacterial warfare we have waged over the years has taken its toll, Dockery said. She is speaking specifically about oral health but the same concepts apply to the microbiome as a whole.

“We have relied too heavily on antibiotics, antibacterial cleansers—and antibacterial mouthwashes to the detriment of our health, all the while thinking that we are helping rid ourselves of undesirable invaders in our bodies,” she said. “Unfortunately, some of those bacterial victims are actually the ‘good guys.’”

INGREDIENTS

Probiotics: An answer to whatever bugs you

It should be apparent that any conversation about functional ingredients and the microbiome has to start with probiotics.

Probiotic comes from the Greek meaning “for life.” Most probiotic organisms belong to the Lactobacillus and Bifidobacterium genera. The former contains about 80 recognized species, with the most well-known and studied being Lactobacillus acidophilus, while the latter is the most abundant genus of good bacteria in the human gastrointestinal tract. Probiotics are primarily bacteria but some species of yeast, such as Saccharomyces, are also counted among the good guys.

Lactobacillus, in particular, has been the subject of serious medical research for more than a century. Nobel Prize-winning Russian zoologist Élie Metchnikoff, best known for his work in immunology, proposed that aging is caused by toxic bacteria in the gut and that lactic acid could prolong life. He even attributed the longevity of the residents of the Balkan countries to the regular consumption of Bulgarian buttermilk, which he himself imbibed daily.

Probiotics certainly enjoy the most name recognition among consumers for gastrointestinal health, and there are positive signs that customers recognize other health benefits as well, according to industry experts.
“The idea behind probiotics, the idea that we might be able to give ourselves beneficial bacteria that improve our health, that idea has a lot of potential, and it is solid.” — Ed Yong, science journalist

“Our DuPont proprietary consumer research indicates that consumers have very positive sentiments about probiotics,” noted Megan DeStefano, Probiotics Global Marketing leader for DuPont Nutrition & Health. “They associate them first with digestive health, but immune health is a close second— consumers know probiotics have benefits there.

“So, I believe these positive probiotic sentiments will pretty easily transfer to other health indications as well,” she added. “That brings me back to educating more consumers on probiotics— the biggest benefit will come from expanding the consumer base.”

Probiotics, as we will learn, are thought to influence a whole field of diseases and conditions of an out-of-balance microbiome: asthma, allergies, dental caries, ulcers, hepatic encephalopathy, urinary tract infections, vulvovaginal candidiasis, dermatitis, inflammatory bowel diseases, diabetes, heart disease, obesity and cancers.

Science writer Yong in his interview with NPR’s Gross made his skepticism about health claims around probiotics clear in no uncertain terms but conceded there is still a great promise in probiotics.

“A lot of these [probiotic] species are being chosen for historical reasons because they’re easy to manufacture and package, not because they’re excellent at establishing themselves in the gut,” Yong argued. “And often they’re very industrialized, very proprietary strains. You know, they enter and then they disappear or they pass through. They don’t have a huge amount of impact. And yet, the idea behind probiotics, the idea that we might be able to give ourselves beneficial bacteria that improve our health, that idea has a lot of potential, and it is solid.”

Reports on the survival and effectiveness of ingested microorganisms in the gastrointestinal tract are mixed, as the microbes often do not survive the highly acidic gastric environment. Many companies have addressed this complaint. Sabinsa Corporation, for example, has produced LactoSpore®, a preparation containing viable spores of \textit{B. coagulans} (formerly known as \textit{L. sporogenes}). This species forms spores, helping it survive the stomach’s acid rain.

“Gut health has always been in top five health concerns for people and that has fueled a lot of research on the application of spore-forming probiotics in recent times,” explained Anurag Pande, PhD, vice president of scientific affairs at Sabinsa. “The unique thing about marketing at Sabinsa is that much focus of the marketing is on the evolving science on the product and how that science can translate into better health for people.”
Health Canada, the Canuck’s version of the Federal Drug Administration, appears to agree with the research. In September, it issued a Product License to Sabinsa for a significant health claim on LactoSpore® Balance: “Helps relieve abdominal pain associated with IBS (Irritable Bowel Syndrome).”

Prebiotics come to the fore of microbiome health

It should come as little surprise then that one-third of Americans are trying to consume probiotics, according to a 2016 Food & Health Survey: Consumer Attitudes toward Food Safety, Nutrition & Health commissioned by the International Food Information Council (IFIC) Foundation. What may be surprising is that 10 percent are also trying out its lesser known counterpart—prebiotics.

In a poll commissioned by AIDP Inc. of 400 diet supplement users, more than 38 percent said they would be very likely or somewhat likely to try a prebiotic with strong digestive and immune health benefits, if the product were science-validated by research conducted at and published by a major university. The survey revealed that 44 percent of these consumers had tried a probiotic supplement.

“As a gut-health ingredient, probiotics is still leader of the pack, but give it some time and prebiotics will soon get there also,” said Alan Rillorta, director of protein & branded ingredient sales for AIDP. AIDP has a relatively new prebiotic called PreticX™, a xylooligosaccharide (XOS) that is non-GMO verified and has been clinically shown to increase Bifidobacteria in the colon and aid in healthy digestion, according to Rillorta. “We think that eventually, with more probiotic products including prebiotics in formulation, the message will spread that prebiotics are selective food for probiotics.”

That’s the definition of prebiotics in a nutshell: nondigestible carbohydrates that serve as food for probiotics. They are naturally found in foods such as garlic, onion, banana and whole grains. Together with probiotics they form a synbiotic, which is a food that includes both the friendly bacteria and the prebiotic fuel they need to survive. This synbiotic effect is common in fermented foods, such as yogurt and kefir.
“As a gut-health ingredient, probiotics is still leader of the pack, but give it some time and prebiotics will soon get there also... the message will spread that prebiotics are selective food for probiotics.”
— Alan Rillorta, AIDP

The prebiotic ingredients market consists of a number of tongue-twisting naturally derived and synthetic ingredients with names like fructooligosaccharides (FOS), inulin, mannan-oligosaccharides (MOS), xylooligosaccharides (XOS) and galactooligosaccharide (GOS).

Steve Hanson, CEO of consulting company GRIP IDEAS, wrote a column in NutraIngredients that said prebiotics is a hot and emerging market, worth about $3 billion today, with predictions that it will experience double-digit growth through the end of the decade. He said food and beverage use accounts for about 80 percent of the market, followed by dietary supplements and animal nutrition.

There is a growing body of scientific literature pointing to the value of prebiotics beyond the gut.

A 2014 study by the University of California-Los Angeles on PreticX involving 32 participants found that “good” bacteria, like Bifidobacterium, increased in two groups that took the prebiotic supplement, while harmful bacteria such as Clostridium did not change. The study also found that PreticX changed the environment of the gut, specifically for bacteria associated with obesity and diabetes, hinting at possible treatments for these types of metabolic diseases.

In a study out of the United Kingdom, a proprietary prebiotic blend called Bimuno, a transgalactooligosaccharide (B-GOS, for short) from New Jersey-based company Clasado, found that the prebiotic helped to enhance the immune system in elderly subjects by boosting Bifidobacterium in their microbiota. This immune-boosting bacteria typically declines in older populations. Subjects showed higher levels of anti-inflammatory response following the consumption of B-GOS.

“Our product is radically different from other prebiotics, which is why we’re seeing these interesting effects in the research we’ve done,” noted Geoff Collins, head of marketing at Clasado, during a recent phone interview.

Collins explained that Clasado scientists developed Bimuno using the enzyme system from the targeted probiotics themselves rather than from a generic enzyme system. Basically, Clasado produced the microbes’ ideal food source, making it easier for them to metabolize and get to work. “It’s the old lock and key approach,” Collins said. “We’ve basically adopted the approach nature might adopt.”
Not the usual suspects

It’s not too trite to say that microbiome research is a new frontier in medical science. There are still discoveries to be made. Both academics and industry scientists will continue to focus on those areas that show the most promise, while a few of the more intrepid will push the research into less well-known areas of the field. A handful of studies have emerged that show other functional ingredients may be linked to the microbiome.

FIBER: In broad terms, all prebiotics are dietary fiber but not all dietary fiber is prebiotic. Dietary fibers can be classified into soluble and nonsoluble fibers. Soluble dietary fibers are fermented, but usually not in a selective way, but prebiotic fibers are fermented in a selective way, meaning not all soluble dietary fibers are prebiotic. Nonsoluble dietary fibers are not fully fermented by gut flora, while prebiotic are fully fermented, again meaning that not all nonsoluble fibers are prebiotic.xii

All of that to introduce one particularly interesting ingredient that research suggests show some prebiotic properties— soluble corn fiber, which has been on the U.S. market since 2007 and is produced from corn through enzymatic hydrolysis of corn starch.xiii

A pair of studies out of Purdue University just this year suggested that supplementing with soluble corn fiber at two critical times in a woman’s life— adolescence and post-menopause— helps the body better absorb calcium to help build and retain calcium in bone. In post-menopausal women, calcium retention improved by up to 7 percent, an amount that would equal and counter the average rate of bone loss in that group. In adolescent women, supplementation with soluble corn fiber improved calcium absorption by 12 percent, which would build 1.8 percent more skeleton a year.xivxv

“Most studies looking at benefits from soluble corn fiber are trying to solve digestion problems, and we are the first to determine that this relationship of feeding certain kind of fiber can alter the gut microbiome in ways that can enhance health,” said Connie Weaver of Purdue University whose work in these studies was supported by Tate & Lyle Ingredients America LLC., which produces PROMITOR™ Soluble Corn Fiber. “We found this prebiotic can help healthy people use minerals better to support bone health.”
Purdue’s Weaver has led four studies in collaboration with Tate & Lyle, which is planning to conduct further clinical studies on the health benefits provided by fibers in the adolescent population across regions that are systematically deficient in calcium intake, according to Andrew Hoffman, director of health and wellness product development at Tate & Lyle.

“Many consumers and manufacturers are familiar with the terms probiotics and prebiotics, and to some extent, they understand that both provide digestive health benefits,” he said. “As more research is completed on the human gut microbiome and the health benefits of our soluble fibers, we anticipate more opportunities to educate consumers and manufacturers on these added benefits.”

Michelle Braun, PhD, a research scientist with DuPont Nutrition & Health highlighted fiber ingredients in the DuPont Nutrition & Health portfolio that have also been shown to support the microbiome. She said studies have demonstrated the ability of both soy fiber and polydextrose to support health in ways traditionally associated with fiber consumption, such as laxation, but have “also been demonstrated to increase fermentation in the colon and short chain fatty acid production. Polydextrose feeds the good bacteria throughout more of the digestive tract. Litesse® polydextrose is a soluble fiber, while FIBRIM® soy fiber is an insoluble fiber that exhibits properties similar to a soluble fiber.”

**Magnesium**: Magnesium is an abundant and busy mineral in the body. It is a cofactor in more than 300 enzyme systems that regulate diverse biochemical reactions in the body, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation, according to the Office of Dietary Supplements in the National Institutes of Health. Lack of magnesium has been implicated by researchers in a number of diseases, ranging from diabetes and Alzheimer’s—many of the same ones associated with an unbalanced microbiome.

In two related but separate papers published by Danish researchers last year, a six-week study of mice suggested that a magnesium deficiency altered their microbiome and caused symptoms of anxiety and depression. In one analysis, the researchers compared mice fed a standard diet versus a magnesium-deficient diet, followed by behavioral testing to evaluate depressive-like behavior, along with several biochemical tests. The magnesium-deficient mice were more immobile in a forced swim test and had an altered microbiome. In the second analysis, the magnesium-deficient mice also displayed anxiety-like behavior, as measured by their reluctance to enter a light box in comparison to the control group.

**Can we use magnesium to regulate the human microbiome? The answer is as complicated as the microbiome itself.**
Planet Body: Exploring The Ecosystems Of Human Health

We are born with our mother’s microbiome—well, those who travel naturally down the birth canal—but eventually we develop our own unique zoo of microbes. The composition of the gut microbiome is constantly in flux based on diet. Such changes can be felt from our head down to our feet.

It’s mostly in your gut—and your head

The term “gut feeling” has taken on a more literal meaning in the last decade or so, as dozens of studies have found a strong link between the gut microbiota and nervous system. An unhealthy microbiome (gut dysbiosis) may be causing mayhem in a wide range of mental illnesses, including neuropsychiatric conditions such as autism spectrum disorder and schizophrenia among them. Scientists also suspect a maladapted gut microbiome may play a role in depression, anxiety and other mood disorders as well.

For example, in a study published in May of this year in the journal Translational Psychology, scientists looked at early-life stress (ELS) on infant rats through maternal separation. One set of rats received a probiotic formulation of L. rhamnosus and L. helveticus in their drinking water that was previously shown to reduce gastrointestinal dysfunction. The untreated infants exhibited an adult-like profile of long-lasting fear memories and fear relapse following extinction, according to the researchers, while the probiotic-fed rats exhibited age-appropriate infantile amnesia and resistance to relapse.

“Overall, probiotics acted as an effective and non-invasive treatment to restore normal developmental trajectories of emotion-related behaviors in infant rats exposed to ELS,” they wrote. “These results provide promising initial evidence for this novel approach to reduce the risk of mental health problems in vulnerable individuals.”
The same researchers, in September, published a second paper in the journal Physiological Science that demonstrated stress and anxiety can even be passed down through generations. The researchers subjected the infant rats to the same early-life stressor of maternal separation. Those subjects, in turn, had male offspring that also exhibited aversion behaviors even though they were not exposed to maternal separation. Once again, probiotics appeared to come to the rescue: “These generational effects were reversed by probiotic supplementation, which was effective as both an active treatment when administered to infant rats and as a prophylactic when administered to fathers before conception.”

In an unrelated study, German and U.S. researchers wiped out the gut bacteria of mice with a powerful cocktail of antibiotics and observed that the rodents had poorer memories compared to the control group. However, the team also showed that it was possible to restart neurogenesis, the creation of new neurons in the brain, by giving the mice a probiotic or making them exercise.

It’s way too early to inundate consumers with ideas about neural regeneration. It’s better to keep it simple, according to Bérengère Feuz, marketing group manager for Lallemand Health Solutions, which has more than 450 probiotic formulations, including many targeting areas outside of gut health. Feuz recommends emphasizing the more tangible effects of taking a probiotic for a gut-brain disconnect—easing nausea and abdominal pain, for instance.

“This is the first effect people want to experience. This is the first thing you want to communicate on, that probiotics can decrease the negative feelings associated in the gut with stress,” Feuz said.

Lallemand developed a product called Probio’Stick® that combines two proprietary probiotic strains, Lactobacillus Rosell-52 and Bifidobacterium longum Rosell-175 with a micro-encapsulation technology (Probiocap®) for what it calls mood-balance applications. It is backed by numerous preclinical studies and two human trials that showed its potential against stress and mood disorders.

“This is the first effect people want to experience. This is the first thing you want to communicate on, that probiotics can decrease the negative feelings associated in the gut with stress.”

— Bérengère Feuz, marketing group manager for Lallemand Health Solutions
The first clinical study, in 2008, was the first human trial that suggested probiotics could relieve gastrointestinal problems associated with stress\textsuperscript{xxiii}, according to Feuz. The pivotal moment came three years later, when researchers in a separate clinical study observed a decrease in urinary-free cortisol levels in the probiotic-treated group.\textsuperscript{xxiv} Cortisol is a biomarker for stress and anxiety. The study has been cited more than 230 times since, Feuz noted.

“For the first time in history … you could see an important drop in a stress, anxiety and depression biomarker,” she said.

In April 2016, Health Canada approved health claim benefits for Probio’Stick associated with stress, anxiety and mood balance, reputedly making it the first and only probiotic with approved health claims in the gut-brain axis area.

Clasado Biosciences’ prebiotic Bimuno has also shown promise in reducing anxiety. A 2014 clinical trial, published in the journal Psychopharmacology, also showed a reduction in the cortisol biomarker for stress and anxiety in the B-GOS group versus the placebo group.\textsuperscript{xxv}

“Very interesting areas are starting to be unraveled here about the ability to take a nutritional intervention, which impacts the microflora, and have potentially positive impacts on someone’s mental well-being,” Collins noted. “There’s certainly further work planned. This whole area of neuronal health and gut-brain axis certainly holds a large potential for future benefits.”

A few numbers to consider here: Globally, an estimated 350 million people of all ages suffer from depression, according to the World Health Organization.\textsuperscript{xxvi} In a report published in May of this year, Zion Research valued the global depression drug market $14.51 billion in 2014, with revenue expected to hit $16.8 billion by end of 2020. In the condition-specific category, Mood, NBJ put a value of $562 million on the market in 2014, with modest growth in the years ahead.

Not immune to changing perceptions

The link between the microbiota in the gut and immunity is not a new one to science. As New Hope editor Todd Runestad explained in a piece written for NBJ: Microbes compete for space within the inner walls of the intestines, and it’s better to have good microbes living in those walls than bad pathogens or toxins. Having probiotics populating the intestinal lining increases the life span of cells that make up the all-important intestinal wall, tightens the junctions between cells that make for enhanced integrity of the intestinal wall, and improves the function and protective responses of the intestinal lining, including inflammation issues within the GI tract. This is at the core of the body’s immune response.
In one sentence from the experts “It is now becoming clear that beneficial bacteria provide colonization resistance to pathogens.” This is from researchers at the Department of Microbiology and Molecular Genetics and Institute for Immunology at the University of California-Irvine School of Medicine in a May 2015 review published in the Journal of Immunity. xxvii

A number of experiments involving microbe-free mice provide scientists an ideal laboratory in which to discover what microbes are involved in immune response, and whether the result is an inflammatory or anti-inflammatory. As Yong explained on NPR: “We can see that certain microbes can actually tune down inflammation, which is an odd concept, because I think we think of microbes as foreign, as other, as things that trigger [inflammation]. Whereas we see with rodent experiments that some species that live with us are actually capable of quenching inflammatory fires, so they are capable of calming the immune system and saying, ‘I come in peace.’”

Earlier this year, Spanish researchers analyzed the influence of gut bacteria on immune recovery in HIV-infected patients undergoing antiretroviral treatment and discovered a correlation between immune recovery and the behavior of a certain subset of gut bacteria in response to treatment. xxviii They reported in eBioMedicine journal that gut bacteria appear to play a role in successful immune recovery in HIV-infected individuals, according to reprint of the news release on ScienceDaily.

Antiretroviral treatments might have a greater impact on HIV patients’ health if combined with therapies that target a subset of beneficial bacteria. “The design of new probiotic foods could be an option, for instance,” said co-author Manuel Ferrer of the Catalysis Institute in Madrid.

In another recent study out of Duke University, scientists highlighted the links between the gut, the brain and immunity. By manipulating dopamine signaling in the nervous system of the nematode worm C. elegans, they were able to control inflammation in the gut. The study, which appeared in Current Biology, offered some evidence that the immune system can be controlled using drugs originally designed to target the nervous system. xxix
Studies on some the ingredient industry’s most popular products have shown some positive results in recent years. For example, among the 20 published studies on GanedenBC30, one found anti-inflammatory properties in the gut, while another study found BC30 significantly increased T-cell production of TNF-alpha, a marker for inflammation, upon exposure to various viruses.

Clasado’s Collins said there is particular interest for his company’s prebiotic with immunity benefits for infant formula.

Many studies have emerged that suggest the first six months or so are critical for the development of a baby’s microbiome. For example, infants born by caesarian section do not pick up their mother’s bacteria, with some research suggesting they are more likely to develop asthma or allergies later in life. Some of the C-section mothers have insisted on having their child immediately swabbed with vaginal fluid after birth, in an attempt to pass on beneficial bacteria to their newborns. Scientists in the British Medical Journal have warned against so-called vaginal seeding due to threat of infection, according to an article in The Guardian.

Selling the idea of immunity health in the form of a probiotic pill or a chocolate bar containing prebiotics is becoming an easier one in the Americas and Europe, where such supplements have traditionally been associated with gut health. Cultural relativism does come into play, according to Feuz.

“We are facing different situations in different countries. We have learned by experience that it’s really a matter of market maturity in the perception and acceptance of probiotics,” she said. “It’s really cultural. The Chinese market started with immunity and not gut health.

“It’s really a matter of education,” she added. “This is where the mass media is very important.”

In 2012, a Datamonitor global study in 20 markets around the world discovered a sharp rise in interest in immune health, rising to second on the list of health concerns. Further, a staggering 88 percent of consumers are interested in foods and beverages with immune-health benefits, but only 40 percent are actively buying. That translates to a huge opportunity for products that can offer real immune benefits.”
Take a deep breath

There is a growing body of research that shows probiotics and prebiotics that nudge the microbiome one way or the other can also help with a variety of respiratory problems, from upper respiratory infections to asthma to cold and flu symptoms.

Last year, Chr. Hansen made news with the completion of a large clinical study involving more than 1,100 subjects in Denmark and Germany, showing that in cases of influenza-like illness, the number of sick days dropped from eight to five in the group that consumed a daily dairy beverage with one billion live bacteria of L. Casei 431® compared to the placebo group. In addition, the proportion of subjects who required health care support during the follow-up period was 28 percent versus 22 percent.xxxi

In an even earlier study using two of DuPont Nutrition & Health’s HOWARU® Protect Probiotics products, researchers from Australia saw evidence that suggested the probiotic formulations may reduce the risk of and delay the onset of respiratory illness, as well as improve training load during physical exercise. In the healthy men and women who consumed a daily probiotic dose over the five-month study period, the risk of upper respiratory tract illness was reduced by 27 percent for the group taking HOWARU Protect Adult.xxxii

The company just completed additional research on probiotic supplementation on respiratory illness in collaboration with researchers at the University of Virginia, according to Braun. More than 100 healthy adults participated in the clinical trial, where Bifidobacterium animalis subsp. lactis BI-04TM— known commercially as HOWARU® Protect Adult— was supplemented daily for four weeks, after which rhinovirus was applied to the nostrils of the volunteers to induce a mild cold. The results will be published soon, she said.

Lallemand out of Canada has its own success stories. During a six-week human clinical study published in 2015, scientists found a greater number of “healthy days” and a lower number of colds and flu days with patients taking the company’s B. bifidum Rosell-71 strain.xxxiii

It’s not just probiotics that seem to have a modulating effect on various respiratory symptoms. In an August 2016 study led by Nottingham Trent University, researchers found that Bimuno from Clasado tamed exercised-induced asthma.
In the double-blind crossover study, 10 participants with exercise-induced asthma and eight control participants without asthma randomly received B-GOS or a placebo for three weeks. Participants undertook a hyperventilation test in the laboratory, which causes reductions in lung function replicating the symptoms and severity associated with exercise-induced asthma. The falls in lung function after the hyperventilation test were compared after three weeks of prebiotic B-GOS and placebo. Blood tests also studied circulating markers of airway inflammation.

Participants receiving B-GOS demonstrated a dramatic reduction in the severity of exercise-induced asthma. “We were calming the immunity response and relaxing the bronchial,” Collins said of the results. “When you take our product, you significantly reduce that reaction. … It opens up another area of research linked to our ability to modulate the microbiome but have this impact on the immune and inflammatory response.”

Some numbers to consider here: From 2001 to 2011, the number of people with asthma grew by 28 percent, according to the Asthma and Allergy Foundation of America. This constant rise in asthma means the cost of asthma has also grown. In 2002, the total cost of asthma in the United States was $53 billion. In 2007, the cost of asthma grew to $56 billion.xxxv In the U.S. alone, influenza costs the economy between $71 and $167 billion per year, according to the World Health Organization.

And open wide …

Time to move not just beyond the gut but completely out of it. The mouth, an extension of the digestive tract, is the obvious place to begin, according to Stratum’s Dockery.

“The industry has done a very good job in educating manufacturers and the end-consumer regarding the benefits of specific strains of bacteria in the gut; and now it is our job to increase the realization that self-protection of the body begins in the mouth, where most of the pathogens that make us sick enter,” she explained. “If we want to protect our home, we install a security system at the entry points into the house, not just a lock on our living room or bedroom door.”

Stratum Nutrition, which markets the oral probiotic BLIS K12® developed by New Zealand company BLIS Technologies, boasts several clinical trials among nearly 20 studies on ears, nose and throat illness, that show the effectiveness of BLIS K12. The latest study looking at BLIS K12, a rare strain of Streptococcus salivarius, suggests that the oral probiotic may help prevent pharyngo-tonsillar infections, or recurrent tonsillitis, in children.
“We are just beginning to open the door (or mouth as it may be) to the many benefits that the BLIS probiotics provide, as this knowledge grows, so will our understanding of the total human microbiome that extends far beyond the confines of the gastrointestinal tract.”

— Nena Dockery, technical services manager at Stratum Nutrition

Results of a 2016 study published in the journal *Therapeutics and Clinical Risk Management* showed that 88 percent of the group that received BLIS K12 experienced no pharyngo-tonsillar infections compared to only 22 percent of the untreated group. Even nine months after the use of BLIS K12 had been stopped, the development of new pharyngo-tonsillitis infections was significantly lower when compared to the period before treatment.xxxvi

Dockery said BLIS probiotics work best as standalone dietary supplements that can be given in the form of lozenges or chewable tablets, to ensure adequate time for the bacteria to look for a suitable home in the oral cavity. However, BLIS Technologies recently received a non-objection letter from the FDA in response to their GRAS self-affirmation submission for BLIS K12.

“This definitely clears the way for multiple applications in food products, such as yogurt or ice cream,” Dockery said. “I can’t think of a better way to get the benefits of BLIS K12 than in a scoop of cold, delicious ice cream.

“We are just beginning to open the door (or mouth as it may be) to the many benefits that the BLIS probiotics provide,” she added. “As this knowledge grows, so will our understanding of the total human microbiome that extends far beyond the confines of the gastrointestinal tract.”

It’s what’s on the outside that counts

The skin is the body’s largest organ, it’s also one of the most diverse microbial ecosystems: The human armpit is akin to a swamp, for example, while other parts are like a desiccated desert, with different bacteria and other microbes taking up residence in their particular niche.xxxvii

Researcher Elizabeth A. Grice, with the University of Pennsylvania’s Perelman School of Medicine, has published extensively about the skin microbiome. In a 2014 published report entitled “The skin microbiome: potential for novel diagnostic and therapeutic approaches to cutaneous disease,” she suggested that both probiotics and prebiotics may hold potential as therapies for skin diseases.xxxviii

For more information, visit www.blis.com or call 1-888-BLIS-USA.
“Probiotic applications, where the skin microbiota is supplemented with a beneficial microorganism, may offer promise for treatment of conditions such as acne,” she wrote. Another possible application is for that old BO: “Deodorants containing probiotics and/or prebiotics may in the future be a feasible strategy to combat body odor, where odor-producing bacteria would be competed away with recolonization by non-odor producing bacteria.

“More research is needed to identify probiotic strains and prebiotic substrates that may benefit skin microbial communities, and thus skin health,” she noted.

Consumers are not just interested in fighting acne and bad odors; they want to tussle with Father Time itself. NBJ values the anti-aging supplements market at more than $400 million.

There is a growing interest in using probiotic technology in personal care and beauty products for just such a purpose, according to Gandeden’s Bush, which he said led to the launch of the probiotic byproduct called Bonicel in 2012. Clinical trials with human participants showed that Bonicel reduced the appearance of seven signs of aging, he said, such as reducing the appearance of fine lines, wrinkles, pore size and the appearance of redness while increasing skin moisture and elasticity.

“In a separate gene-regulation, full-thickness skin model study, Bonicel was also found to increase the expression of a gene relating to collagen production, which provides further support that Bonicel may have skin firming and antiwrinkle activity,” he said. “Since its introduction, Bonicel has continued to be pushed out to top beauty companies, and has already been included in products from well-known companies such as Murad and others. Just in the past few months, three new lines of products containing Bonicel were launched.”

Sabinsa’s Pande noted that the personal care market today is flooded with antimicrobial soaps, creams and gels that promise to eliminate germs without considering the bigger consequences. “However, skin is not just inhabited by pathogens; several hundreds of useful microorganism also live there,” he said. “In fact, skin has its ecology that is diverse and differs from person to person. Our skin health does not depend only on whether we get rid of the bad bacteria; it is dependent on maintaining healthy balance between good and bad bacteria.” (About a week after this interview, the FDA announced its ban on 19 specific active ingredients used in these antibacterial products.)

One of the challenges in marketing personal care products is tempering expectations with actual results, noted Shaheen Majeed, Sabinsa’s marketing director.
“There’s a certain notion that most creams and lotions are supposed to work miracles, once applied, people expect instant success,” he explained. “Well, you can’t take one probiotic pill and call it a day. No matter which probiotic, their respective mechanism of action has to take place over several doses and courses of interaction with your gut. Likewise, the use of beneficial bacteria on your skin … requires necessary use and re-use.

“All this, based on scientific documentation and proof of cosmetic-based probiotic product concepts, will ease the challenges the manufacturers have and the consumers have,” he added. “Right now, consumers are hungry for probiotic products; the right data can help feed their skin needs.”

But it’s what’s on the inside that is getting a lot of attention

Could the next big diet craze involve the microbiome? There is intriguing evidence that altering the gut microbiome may help prevent weight gain and protect human health from a range of related diseases such as diabetes, fatty liver disease and atherosclerosis, the hardening and narrowing of the arteries. More than a third of U.S. adults are obese.

In a study presented at an American Physiological Society conference this summer, researchers discussed how incorporating engineered bacteria into the guts of mice both kept them from gaining weight and protected them against some of the negative health effects of obesity. The engineered gut bacteria produce a small lipid that helps suppress appetite and reduce inflammation. People who are obese typically produce less of this lipid, which is made by the small intestine.

“We have previously shown that this approach with engineered bacteria could inhibit obesity when standard mice were fed a high-fat diet,” said Sean Davies, PhD, associate professor of pharmacology at Vanderbilt University who led the study, in a press release. “Our new studies focused on mice highly prone to develop atherosclerosis and fatty liver disease, and we showed that the engineered bacteria were beneficial not only in inhibiting obesity, but also in protecting against fatty liver disease and somewhat against atherosclerosis. … Someday in the future, it might be possible to treat the worst effects of obesity simply by administering these bacteria.”
“This study was the first to investigate the ability of soy to modify the gut microbiota composition and further explore how those changes relate to expression of genes in the liver that are involved in lipid metabolism. The potential mechanism behind soy’s ability to improve lipid concentrations, lowering LDL and total cholesterol, without lowering HDL remains an area of investigation.”

— Michelle Braun, PhD, a research scientist with DuPont Nutrition & Health

Earlier this year, a study by the University of British Columbia revealed that prolonged exposure to antibiotics can accelerate the development of type 1 diabetes by disrupting the community of microorganisms that live in the human digestive tracts, Health Newsline reported. The science has proved convincing enough that companies are investing heavily in microbiome research related to metabolic syndrome and related diseases. For example, Imperial College London and Nestlé Research recently announced that they are establishing a research and innovation partnership exploring metabolic health and nutrition. Chr. Hansen and Caelus Health announced their own collaboration this year to develop Eubacterium hallii as a next-generation probiotic to prevent and treat metabolic syndrome.

The potential health benefits in the area of metabolic syndrome could be a game-changer, according to Sanders. “To help people from making that transition from pre-diabetic to diabetic would be huge,” she said, though cautioned that obesity is a complicated area of research: “I think it’s going to take a lot of teasing out before we understand how to work in that area. I think there’s potential.”

It’s not just probiotics that are showing promise in altering the gut microbiome in ways that affect metabolic health.

A study first published March 2016 in The Journal of Nutrition found that a soy diet contributed to a more diverse microbiota than a diet from milk protein sources. The study was the first to investigate the ability of soy to modify the gut microbiota composition and further explore how those changes relate to expression of genes in the liver that are involved in lipid metabolism, said DuPont’s Braun. “The potential mechanism behind soy’s ability to improve lipid concentrations, lowering LDL and total cholesterol, without lowering HDL remains an area of investigation.”
The investigators, led by Elaine Krul, PhD, senior technical fellow at DuPont Nutrition & Health, fed hamsters a diet mimicking the composition of a typical Western human diet containing either milk protein isolate or one of three differently processed DuPont Danisco® soy proteins. Researchers then observed the diets’ effects on blood cardiometabolic measures, microbiota composition in different sections of the gut, and expression of genes in the liver that are involved in lipid metabolism.

“The soy-fed hamsters had a more diverse microbiota than those fed the milk diet,” Braun said. “Also, differences in abundance of several key microbial families were associated with beneficial changes to lipid concentrations for SUPRO® soy protein only.”

Companies like Clasado and AIDP that are marketing prebiotics are also seeing positive results when it comes to biomarkers of metabolic diseases.

A February 2013 published study found several biomarkers associated with metabolic syndrome improved over the month-long clinical trial involving B-GOS. “Many of the markers were changed back to levels that you would see in a normal weight individual. Clearly the microbiome is playing an important role in people’s metabolism but also whether they’re in a health state when they’re overweight,” Collins said. “That seems to reinforce the idea that if you can change the microbiome, you can have a profound impact on metabolism.”

Currently, AIDP primarily markets PreticX™, its range of XOS (xylooligosaccharide) prebiotics, for general gut health. “Although formulators and marketers are just as quick to recognize our clinical data supporting more specific benefits of PreTicX in the areas of weight management, blood lipid control, and blood glucose levels,” said Rillorta for AIDP.

A 2014 UCLA study in humans showed that PreticX at low dosage significantly modified gut microbiota, helping to grow more species of good gut bacteria in both healthy people, and those who are overweight or with higher blood glucose levels, according to Rillorta. “Our 2014 UCLA study demonstrated XOS favors a Firmicutes to Bacteroidetes ratio optimal to weight management,” he noted. “In another 2006 study, PreticX showed significantly decreased serum triglyceride, cholesterol and blood glucose levels.”

AIDP recently gained organic certification for its PreticX brand, which is already certified non-GMO and FDA-GRAS. The choice to pursue organic certification was a no-brainer, according to Rillorta, who points to the $43.3 billion in U.S. organic sales in 2015 as an obvious motivator. “Furthermore, statistics show that organic is one of the quickest growing sectors of the U.S. food industry, with a track record of consistent double-digit growth year-over-year,” he said. “I mean, with these type of numbers we would be crazy not to establish our own organic footprint.”
A mention of the unmentionable

Women’s health is one of those topics that has become strangely politicized in recent years. Politics aside—or perhaps because of?—there is surprisingly a dearth of research on vaginal microflora. Scientists do know that the microbiome plays an essential role in women’s health. Infections such as bacterial vaginosis or urinary tract infections are often linked to unbalanced vaginal microflora.

Bacterial vaginosis is a condition that can have important implications for reproductive health at many levels, according to the Mayo Clinic’s Center for Individualized Medicine’s Microbiome Program. Mounting evidence suggests it may be a result of critical changes in the local microbiome.

“There is good evidence supporting the use of L. acidophilus or yogurt enriched with L. acidophilus for the treatment of vaginal infections,” according to the Mayo Clinic. “More evidence is needed to support the use of L. acidophilus in treating vaginal yeast infections such as candidiasis, as well as restoring microorganisms in the vagina after treatment for infections. Several studies have used L. acidophilus in combination with other probiotics or supplements, such as vitamin B.”

Lallemand offers specific probiotics of the Lactobacillus species for vaginal microbiome health, particularly focused on vaginal infection. “There could be many more applications in this area,” Feuz said. “Women are conscious about the problem and they are constantly looking for solutions. This is where probiotics can be helpful.”

A crowd-funded company launched in 2012, uBiome provides a relatively inexpensive kit for collecting data on an individual’s microbiome. The company recently announced a study to investigate how the vaginal microbiome changes over the course of the menstrual cycle, and during different phases of life. The company said the research will help discover how the vaginal microbiome is affected by monthly cycles to advance research in this understudied area.
Beyond the Microbiome

Putting consumers in charge of the lab

uBiome certainly isn’t the only game out there for those wishing to delve into their personal microbiome and contribute to the ever-growing research in the field as citizen-scientists.

The American Gut Project, another crowdsourced microbiome project established in 2012, claims to be one of the largest citizen-science programs in the United States. Its goal is to build a comprehensive map of the human microbiome. To date, it has enlisted more than 8,500 people to participate, raising nearly $2 million to cover the cost of processing, sequencing, and analyzing samples sent to the lab. In return for their samples (and $99), participants receive an overview of how their microbial profile compares to other participants, along with a full list of the bacteria and relative abundance found in a participant’s sample.

In an interview posted on ResearchGate, project researchers Embriette Hyde and Rob Knight said that among the findings so far are that the “strongest associations are with the country you live in, the number of types of plants you eat in a typical week, and how much sleep you get each night. We’ve also noticed that exercise frequency, alcohol consumption, and the number of bowel movements one makes in a day are also linked to microbiome diversity.”

A slightly different twist to the citizen-science approach was announced in August of this year by biotech company ISOThrive, which produces a concentrated soluble prebiotic fiber through natural fermentation called Prebiotic Nectar. In partnership with uBiome, ISOThrive launched its Gut Health Challenge in which consumers can test their microbiome before and after taking a 30-day or 90-day supply of ISOThrive Prebiotic Nectar. Money back guaranteed, of course.
In the end, fecal transplants offer great promise

Until companies develop the world’s most powerful probiotic yogurt or a prebiotic pill that defeats diabetes, one of the most effective therapies targeting the microbiome to date has been fecal transplant therapy.

Insert your poo jokes here, and let’s move on.

The purpose of a fecal transplant is to replace good bacteria that has been killed or suppressed, usually by the use of antibiotics. This causes bad bacteria, specifically Clostridium difficile, or C. diff., to overpopulate the colon, according to the Fecal Transplant Foundation. This infection causes a condition called C. diff. colitis, which can cause debilitating, even fatal, cases of severe diarrhea.\textsuperscript{xlvii}

The Centers for Disease Control reported that about 347,000 people in the United States alone were diagnosed with this infection in 2012. Of those, at least 14,000 died.\textsuperscript{xlviii}

In a previous interview with New Hope’s Natural Foods Merchandiser, Perlmutter said that fecal transplants are being used to treat other diseases related to inflammation and autoimmunity. There is also evidence that the procedure, which has FDA approval, may prove helpful in various neurological issues like multiple sclerosis and even autism.

“Less aggressive, and certainly more palatable for the general population, is the utilization of probiotic enemas. This is actually a very simple technique in which rather than providing probiotics orally, they’re given in the form of an enema,” Perlmutter said. “This is not to say that there is not a place for oral probiotics as new research is demonstrating profound effects of from orally administered probiotics in a variety of clinical situations.”

In fact, ClinicalTrials.gov now lists 176 studies for fecal transplants. The procedure is not a panacea for all diseases, even for those who fall under the metabolic syndrome category. For instance, Polish researchers reported that transplanting a fecal sample from lean, healthy mice to obese ones may affect the gut flora but does not help improve metabolic syndrome symptoms.
The functional ingredients industry is no stranger to criticism and controversy. From the New York attorney general office’s 2015 crusade against supplements companies to the unbending stance taken by the European Food Safety Authority on health claims for ingredients like probiotics, companies in this business often have more to worry about than just their bottom line.

One recurring criticism is that much of the science behind the ingredients is done by the companies themselves. There are the obvious motivations— businesses are for-profit, after all— but the time and expense to manage a research program and fund clinical studies is no small matter. In some ways, companies fill a niche that research universities either overlook or don’t have the resources to apply.

Studies on probiotics are one prime case. Few universities are going to have access to the materials or expertise of supplement companies, some of which have spent decades testing and retesting their strains, which can be quite rare.

For example, most of the clinical trials for the BLIS oral probiotics have been conducted by customers or by BLIS Technologies, according to Nena Dockery, technical services manager at Stratum Nutrition.

“This is mostly due to the unique nature of the BLIS probiotics,” she explained. “Unlike botanical ingredients for which there may be several sources and widespread use, the BLIS strains are unique. Therefore, there are not as many entities conducting research that might be cited as independent studies. As is the case with most natural ingredients, there is no monetary incentive for pharmaceutical companies or universities to conduct studies.”

Out of nearly 1,000 published paper on the microbiome-gut-brain axis found on PubMed, there are only 35 in vivo studies and 14 clinical trials on probiotics, according to Bérengère Feuz, Marketing Group manager for Lallemand Health Solutions. Three of the clinical trials and 14 of the in vivo studies were done by Lallemand. “It’s not a lot,” she conceded. “We will not stop there, of course, I think there is a lot more to do.”

Not surprisingly, Anurag Pande, PhD, vice president of scientific affairs at Sabinsa, doesn’t agree with people who are critical of industry-sponsored studies.

“There should be a healthy balance of industry-backed and independent studies carried out at renowned universities,” he said. “If there is a claim which industry has found to be path-breaking, it is usually expected to be validated by third-party studies, which can be university or any independent research institutions.”

continued on next page
He noted that Sabinsa allocates its R&D budget along the lines of the pharmaceutical industry, methodically carrying out in vitro, in vivo, preclinical and clinical experiments.

“These studies can bring early momentum to the product to gain both interest of the market and consumers, as well as the academic community. A very good example of this is Curcumin C3 Complex,” he said, referring to one of its flagship ingredients. “Today Sabinsa has over 50 clinical research papers, and while initial studies were done or sponsored by Sabinsa, those studies fueled the interest of academic circles and out of 50 studies, the majority have been done by universities research institutions as independent studies.”

Pande said Sabinsa hopes to take a similar path with LactoSpore, a probiotic with more than 20 studies already completed.

Ganeden Biotech takes a different approach with its research, according to Mike Bush, president of probiotics manufacturer Ganeden Biotech and executive board president of the International Probiotics Association.

“Despite the criticism that company-sponsored studies are somehow skewed, Ganeden only utilizes qualified contract research organizations, universities or other third-party research organizations—we never ‘run’ trials ourselves,” he explained. “We can’t speak to how other companies sponsor studies, but our research is vetted by [independent review boards] to ensure that the studies are well designed, ethical and follow scientific standards, which ensure nonbiased outcomes.”

Dockery said that studies worthy of serious consideration need to appear in peer-reviewed publications whatever the results.

“All too often, developers will conduct studies, but not submit the study design and results for peer review,” she said. “It is difficult to scrutinize study results without reviewing the details of the study. Not publishing a study can often mean that the results of the study were not all that good, or the study design was faulty.”
Conclusions

Research into the microbiome is perhaps one of the most exciting ventures in the medical field this century. There will be disappointments and dead ends, but the possible payoffs for improving human health will drive the science toward new discoveries.

Companies inside and outside the industry are investing in that future. The Wall Street Journal reported in September that venture-capital investment in microbiome companies grew at a faster rate than overall venture-capital funding. From 2011 through 2015, venture funding in microbiome firms soared 458.5 percent to $114.5 million, compared to overall venture investment growth of 103.4 percent to $75.29 billion. “This year, microbiome investment has surged again despite a decline in overall venture funding,” WSJ reported. “The $616.9 million raised for microbiome companies to date so far in 2016 is more than all of the venture investment in the microbiome space in 2011 through 2015 combined.”

Meanwhile, companies like DuPont will continue to engage in research on the effects of the microbiome on digestive health and other conditions, according to Braun. “We are also investigating the microbiome and immune health, particularly support of respiratory health in children and adults. Additionally, we are exploring the microbiome and cardiometabolic health,” she said.

“We are seeing in the recent research that the role of gut bacteria is much wider than we thought,” concluded Pande of Sabinsa. “It definitely stretches beyond the gut walls and may have much more important roles in other aspects of human life such as inflammation, immunity, skin health, cognitive health and even lipid health. … Understanding of [the] microbiome and how changes in the microbiome can [affect] the human health are going to be some of the topics on which probiotic research will be focused going forward.”

Probiotic, prebiotic or some other ingredient yet to be realized— the important thing to the consumer is the end result.

“At the end of the day, what people want to know is whether or not you can modify the microbiome and improve people’s health and prevent or even treat disease,” Sanders said.
Footnotes


New Hope (http://newhope.com/health-conditions/microbiome-revolution-usher-designer-foods)


International Probiotics Association (http://internationalprobiotics.org/resources/essentials/)


Prebiotic Canada (http://www.prebiotic.ca/prebiotic_fibre.html)

FiberFacts.org (http://fiberfacts.org/soluble-corn-fiber/)

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Peter Rejcek is the author of this edition's Deep Dive.

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Stratum Nutrition® is a specialty health ingredient supplier specializing in condition-specific categories which include structural, digestive and immune health to offer full solutions for human, companion animal and equine nutrition. Leveraging the Novus International core competencies in nutritional research and innovation, these ingredients are progressive, safe and reliable. Stratum’s ingredient portfolio includes the following branded ingredients:

- **BLIS K12®, Streptococcus salivarius** (S. salivarius), is one of the most numerous bacterial strains found in the mouth of healthy individuals. However, only a small percent of people have naturally occurring *S. salivarius* with the health-supporting attributes of BLIS K12. The BLIS K12 strain was originally discovered as scientists tracked the oral health of a child with exceptional throat health for several years. Scientists found that a particular strain of *S. salivarius* (or BLIS K12) was associated with ear and throat health. It is now marketed as BLIS K12® as an advanced oral-cavity probiotic. This specific and proprietary strain of *S. salivarius* acts to maintain fresh breath naturally while supporting mouth and upper respiratory tract health.*

- **BLIS M18™** is a friendly bacterium that can be used in conjunction with regular oral hygiene practices to establish a healthy balance of natural bacteria in the mouth to support healthy teeth and gums and overall health. BLIS M18 was developed from a specific strain of *S. salivarius*, which has been shown to help promote a healthy oral microbiota. BLIS M18 begins to work within the oral cavity, its natural habitat, where it competes with other bacteria for space and nutrients to help establish itself as a beneficial microbial population. Because of BLIS M18’s active colonization capabilities and its effects on the microbiome, BLIS M18 helps promote a microbial balance in the oral cavity that supports healthy teeth and gums, and may contribute to overall wellness.*

- **ACTAZIN™** is a whole-fruit supplement ingredient made of the nutrient dense kiwifruit. This Non-GMO Project Verified ingredient comes from the premium New Zealand green Hayward Kiwifruit which naturally contains vitamins, minerals, and fiber. The kiwifruit is a natural source of potassium, copper, vitamins C, E, and K, as well as polyphenols, carotenoids and the kiwi-unique enzyme, actinidin. ACTAZIN uses 4-way action to support digestive health: prebiotics, fiber, polyphenols, and enzymes. As a whole-food with prebiotic activity, ACTAZIN is a good combination for probiotic digestive formulas.*

- **NEM®** is a food-sourced ingredient containing hyaluronic acid, glycosaminoglycans, collagen and other beneficial proteins that support joint health, and it is sustainably derived from eggshell membrane. Clinical trials show that NEM helps maintain joint comfort and flexibility, including a healthy range of motion. These studies showed that subjects were already seeing beneficial results at 7 and 10 days with only 500 mg per day.*

- **ESC®** brand calcium from eggshells is a naturally pure calcium source compliant with FDA, USP, and California Proposition 65 limits for heavy metals at the full 1000 mg dose of elemental calcium per day. Now offered in ESC Organic!