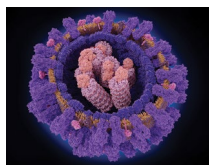


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# Appetite grows for biotech foods with health benefits

A new wave of bioengineered offerings is beginning to capture consumer interest.

**F**oods made with biotech-derived ingredients are reaching the US market with a new motto: health benefits for the masses. On April 1, the fast-food chain Burger King added to its menu a plant-based burger made by Impossible Foods that tastes uncannily like meat, thanks to bioengineered yeast. And a few weeks earlier, Calyxt commercialized an oil free of trans fats from a gene-edited soybean.

The moves demonstrate that newcomers to the biotech food space want to align their products with consumer values, particularly health. They “are much more engaged in the social conversation than we’ve seen historically,” says Charlie Arnot, CEO at The Center for Food Integrity. And for the most part, consumers and the media have responded positively to these small companies with big ideas.

Since the 1990s, agbiotech has been dominated by large multinational seed companies using gene engineering to develop crop traits primarily to meet the needs of industrialized farming. For example, the most common biotech trait, herbicide tolerance, enables growers to spray herbicides indiscriminately on crops, such as maize, soybeans, canola and cotton, killing weeds and not the crop. Despite the popularity of the technology with the farm sector, these products singularly failed to resonate with consumers. “Pouring a bunch of chemicals on crops to produce more so that the farmer is more economical does not make good dinner conversation with grandma or the kids,” says Manoj Sahoo, chief commercial officer at Calyxt. “Companies have not done a good job telling the consumer what’s in it for them.”

About five years ago, a handful of smaller companies sprouted and debuted biotech-derived foods for niche consumer and food-service markets. Today, Okanagan Specialty Fruits grows apples that don’t brown after they are sliced (*Nat. Biotechnol.* **33**, 326–327, 2015). And Simplot sells potatoes



Next-generation Impossible Burger even bleeds, but will consumers be swayed? Credit: Impossible Foods

that don’t bruise easily during storage, and produce less acrylamide—a compound identified as a probable carcinogen—when cooked (*Nat. Biotechnol.* **33**, 12–13, 2015).

But these products didn’t exactly capture consumers’ hearts. “I don’t know that there are a lot of consumers clamoring for a non-browning apple,” says Arnot. “And the whole idea of acrylamide in potatoes—again, that’s pretty technical.” Some of those products also drew criticism because they are considered ‘GMOs,’ or genetically modified organisms.

By contrast, biotech companies developing the newest wave of high-tech food, including those using gene editing techniques such as

CRISPR–Cas9 or transcription activator–like effector nuclease (TALEN), are trying to align themselves with what they perceive as consumers’ most strongly held values. They say their food is healthier, more earth friendly, or more socially conscious than the GMOs before them. And many use genetic engineering techniques that don’t trigger regulatory review and that result in products that might not have to be labeled as bioengineered or GMO in the United States.

One entity at the forefront of this wave of consumer-oriented companies is Impossible Foods. It has embarked on the ambitious goal of replacing animals as a source of meat because, it contends, animal agriculture is

## FBI raids Silicon Valley microbiome startup

Federal Bureau of Investigation (FBI) agents searched uBiome headquarters on 26 April, reportedly investigating questionable billing practices, according to the *Wall Street Journal*. The California Department of Insurance is also conducting an investigation into billing practices at the microbiome startup. uBiome uses machine learning and high-throughput sequencing of the 16S ribosomal gene in bacterial DNA to profile the gut and vaginal microbiome and provide information with clinical utility. The tests identify microbial species purported to correlate with irritable bowel syndrome, chronic fatigue, diarrhea, weight gain and other conditions. Before the FBI raid, uBiome had already accumulated 28 complaints filed between 2017 and 2019 with the Federal Trade Commission. These complaints, revealed through a Freedom of Information Act request, included a person billed for a test taken by their spouse; after flagging the mistake, the couple were charged about \$3,000 more for a test they never took. Another customer was billed over \$2,000 after the insurance company covered only part of the costs.

uBiome was founded in 2012 with \$350,000 from a crowdfunding campaign and later raised up to \$105 million from investors. The biotech launched SmartGut and SmartJane, doctor-ordered sequencing tests for the gut and vaginal microbiomes, respectively, that are intended to be covered by insurance, and a Gut Explorer kit, which is available directly to the public online at \$89. On 1 May uBiome founders Zac Apte and Jessica Richman were placed on leave, and five days later uBiome withdrew SmartGut and SmartJane.

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“We are just wasting time discussing GM technology. We have capacity and brains to deploy the technology.” Florence Mutua, a member of the Kenyan parliament, comments on a proposal to allow local farmers access to genetically modified maize seed, as the country faces a food and water crisis due to drought. (*Cornell Alliance for Science*, 30 April 2019)

“Rather than picking up a pipette and doing a Series A as your strategy for solving the problem, I would spend five years in D.C. cultivating the right politicians to make sure that we have the right circumstances.” Serial entrepreneur Ned David explains why his antibiotic company failed while his company that treats chin fat succeeded. (*STAT*, 14 May 2019)

bad for the environment, eating a lot of red meat isn't healthy, and replacing meat with plant-based alternatives solves both of those problems. “The way to save the planet is to make a delicious plant-based food,” says David Lipman, CSO at Impossible Foods.

The company's first product—the Impossible Burger—consists largely of soy protein, but looks, tastes and even bleeds like beef. The key ingredient giving the burger the singular, ‘bloody’ taste of meat is heme, a molecule found abundantly in animal muscles bound to the protein myoglobin.

Heme can be sourced from soybean root nodules, where it occurs in the protein leghemoglobin. Impossible Foods' founders determined that sourcing heme from soybean plants didn't make sense environmentally or economically, so the company found a way to produce it using fermentation of bioengineered yeast. Company scientists modified *Pichia pastoris* yeast with a gene encoding soy leghemoglobin, along with other genetic modifications related to the yeast's metabolic pathways.

When fermented with sugars, amino acids and vitamins, the yeast synthesizes heme-bound soy leghemoglobin. A separation process breaks open the yeast cells, extracting the protein, filtering away solids and concentrating the liquid, which is blood red in color. The liquid is then mixed with soy protein and a few other food ingredients to make what looks like raw meat and cooks like a burger.

The final recombinant product is indistinguishable from leghemoglobin isolated from soybean and is not labeled genetically modified. Its status as a non-GMO product likely stems from the precedent set decades ago by the fermentation production of chymosin, an enzyme commonly used in cheese making. To produce chymosin, microbes transformed with a bovine gene that encodes the enzyme are fermented, releasing the enzyme, which is then separated and added to milk as a coagulant. The final cheese product is not considered bioengineered.

With a splashy media launch, the Impossible Burger debuted in 2016 at the hip restaurant Momofuku Nishi in New York. Since then it has expanded to hundreds of specialty restaurants and launched in fast-food chains, such as White Castle in the United States and Beef & Liberty in Hong Kong, as well as (intriguingly) ‘organic’ and ‘all natural’ specialty chains, such as Bareburger in the United States.

The new deal with Burger King, with its 7,200 locations in the United States, will more than double the number of restaurants serving Impossible's product, once the rollout is complete, and puts plant-based

burgers in front of a massive number of meat lovers. “It was a strategic goal of ours to go right to the most burgery burger place you could imagine,” says Lipman, whose father was a butcher. “We'd love to be able to satisfy vegetarians and vegans and people who are health conscious. But really our goal is to make a product that everybody is going to want.”

In another corner of agbiotech, seed developer Calyxt, formerly Collectis Plant Sciences, has used TALEN gene editing to develop what it calls “products with purpose.” The company angles itself as focusing on crops that benefit both consumers and farmers. “The consumer is asking: ‘What's in it for me?’ And that's where we think we're able to tell a story,” says Sahoo at Calyxt.

The company's first commercial product, a soybean oil high in oleic acid, contains no trans fats and has a longer fry and shelf life than traditional soybean oil. Calyxt achieved the effect by knocking out the fatty acid desaturase genes *FAD2-1A* and *FAD2-1B* in soybean. That dialed down the production of linoleic and linolenic acids in the plant, while increasing oleic acid to ~80% of the fatty acids (commonly 18%), according to the company. With that kind of fatty acid profile, the oil doesn't have to be partially hydrogenated—a process that creates trans fats—to retain its flavor for an extended period on the shelf and in the fryer. Calyxt markets the oil to the food service industry for frying, salad dressings and sauces.

Pioneer, now part of Corteva Agriscience, developed a similar high oleic acid soybean oil, and now markets it under the brand name Plenish. It too has a longer shelf and fry life, contains about 75% oleic acid and no trans fats, and was generated with alterations to the same gene family (*Nat. Biotechnol.* 28, 769–770, 2010).

But Plenish soybeans were modified using transgenic technology that triggers regulatory oversight and results in a product largely considered a GMO—a term that carries negative connotations in some circles. By contrast, Calyxt altered the genomes of its plants using TALEN, a type of gene editing. As a result, Calyxt's crops don't require regulatory oversight from the US Department of Agriculture. And it's possible that such gene-edited crops won't have to be labeled as GMOs, says Deepti Kulkarni, a partner at the law firm Sidley Austin, on the basis of her interpretation of the USDA's bioengineered food disclosure standards, which were finalized in December.

Being a gene-edited crop tends to kindle some street credibility. “There's been a lot of popular press about the benefits of gene editing” particularly in medical applications, says Arnot at the Center for

Food Integrity. That seems to cast a halo over gene editing in food, he says. Still, gene-edited foods aren't guaranteed to please the public. "Ongoing transparency will be critical for long-term product success," says Robbie Burns, former vice president for health and nutrition policy at the Grocery Manufacturers Association.

A group of about a dozen stakeholders called the Coalition for Responsible Gene Editing in Agriculture, led by Arnot's organization, in November posted [online a communication resource](#) for agbiotech companies. It encourages them to be transparent and to demonstrate benefits of gene editing that align with public values. The resource also provides conversation starters ("If you or someone you know has a gluten sensitivity, gene editing could help"), wording suggestions ("revolutionary"

is bad; "the next iteration" is better) and practical advice ("Challenging strongly held beliefs will cause people to become defensive and dismissive").

More gene-edited products will soon reach consumers. Yield10 Bioscience used CRISPR-Cas9 to develop lines of *Camelina sativa*, or false flax, with enhanced omega-3 oil, and plans to field test them this year. To startups entering the new age of agbiotech, Arnot offers a warning: "Those who fail to recognize the impact of needing broader social acceptance are doing so at their own risk."

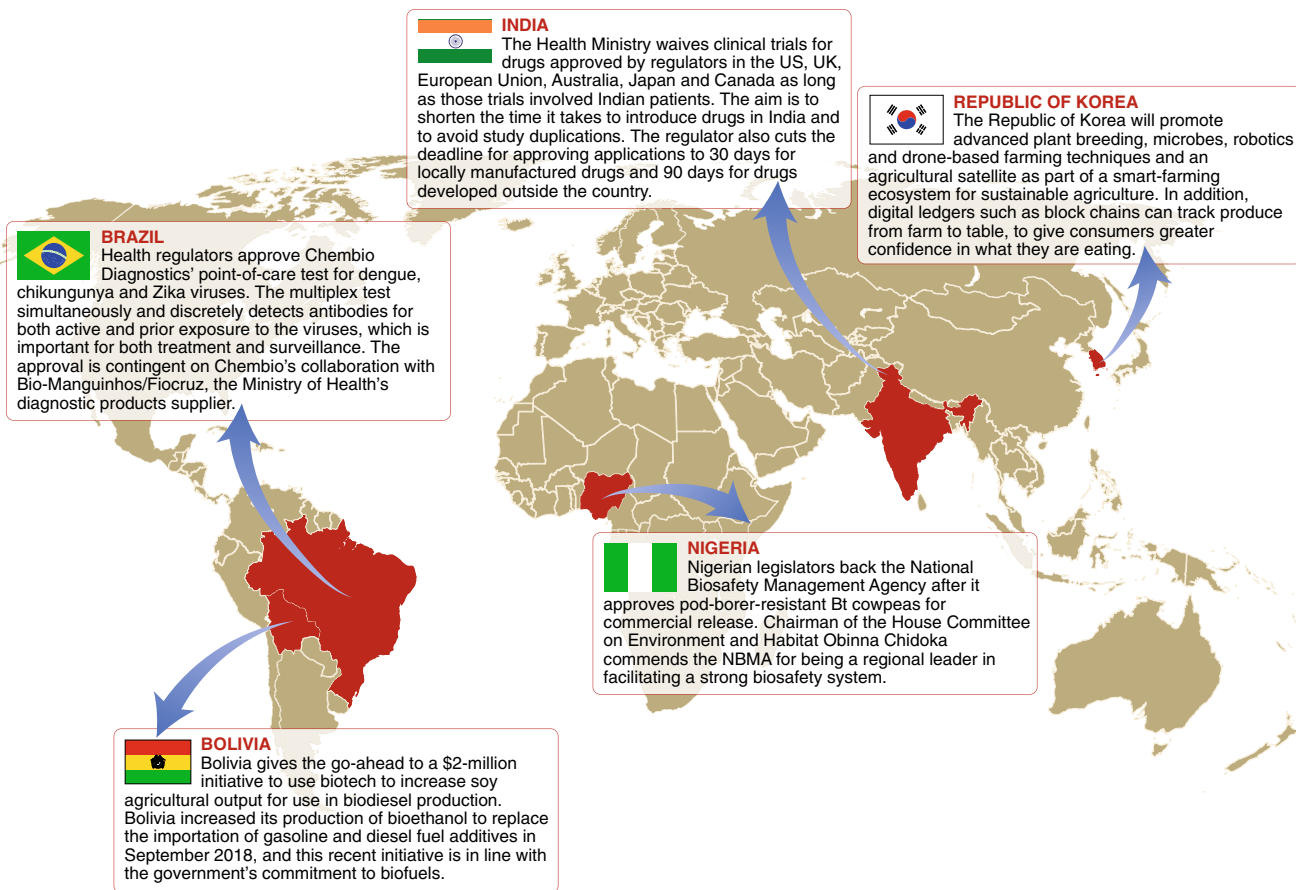
Emily Waltz  
Nashville, Tennessee, USA

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“No matter how Gilead's donation turns out, a majority of patients who would benefit from Truvada—and whose tax dollars helped pay for its development—still won't be able to get the drug.” *The New York Times* editors point out that despite Gilead's donation of 200,000 doses a year of the HIV prevention drug, the donation is likely to do more for the drug maker than for patients. (*The New York Times*, 13 May 2019)

“Just imagine if a never-before-known disease had a clinical trial, and the poor analysts, [who are inundated with gene therapy and immuno-oncology and other things], had to suddenly learn about a new disease and new endpoint. That's very tough for them. And I understand that.” Jeremy Levin, CEO of Ovid Therapeutics, tries to explain why a seldom-used metric for their rare-disease drug for Angelman's syndrome received push-back from analysts. (*STAT*, 6 May 2019)

## Around the world in a month



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