Food for Health Successes and Prospects

Q&A

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Alan Bennett: Martin, you addressed market challenges. Marlin and Jennifer talked about a pipeline—things that are coming through very promising. So, you told us a lot about meeting technical challenges, but what about market challenges—bifidobacteria were mentioned. Can both of you address what you think of the ability of the market to embrace health and nutrition traits.

Jennifer Smilowitz: The *Bifidobacterium infantis* and oligosaccharide combination is more of a medical food approach than something available to everyone at this point. One thing that will be an issue is making claims on prevention, like on food products, and that's not where we are going. We are trying to discover molecular targets, using milk, for health, and the bifido and oligosaccharide combination is just one example. Another business idea is to basically reconstitute HDLs that can bind pathogenic bacteria, but also are still functional HDLs. Now, not all HDLs are the same. Some are actually dysfunctional and some are more functional, and so this could be more of a therapeutic or theranostic approach. But the idea is to use milk, which is the food, in this endeavor.

Marlin Edwards: I should emphasize that all the projects I presented with respect to nutritional or sensory enhancement in vegetables are produced using conventional plant breeding. We use modern technology as a diagnostic tool—molecular markers to understand the native genetics behind these traits, but they are delivered entirely through conventional breeding. So, we don't expect complications in launching those. With respect to the soybean-oil enhancements, of course there is a tradition in this country of acceptance of biotech projects in soybean oil and we are very hopefully that the public will embrace these products as they will have direct consumer benefits.

Bennett: A short follow-up for you, Martin. Your timelines are long and when you are talking about disability adjusted life years that's got to be a frustration. Two questions: Is there any way to accelerate these timelines? And does the Bill and Melinda Gates Foundation have a long-term commitment? Will they see this through to the end?

Martin Fregene: On the timeline, I was asked the same question by my president: "This is too long. I want to see it happen in two years." The truth is, if you are going to give farmers something reliable, you need to test for at least three years, so maybe you could reduce it to about five total, but that is about the minimum. Not less than five. One year to create the event, one year to greenhouse test and then 3 years of field testing. And then on long-term commitment—yes, they are committed over the long haul.

Bennett: And while I have the microphone, I have a quick technical question for you. I'm intrigued by the sporazein trait and the ability to produce protein bodies. What implications does that trait have for nitrogen fertilizer, for example?

Fregene: It's interesting that cassava has tons of nitrogen in the leaves. We aren't taking more out of the soil; we are deploying what is already in the plant—in the leaves and also in the roots—and redeploying it into storage proteins. So far, we haven't seen an effect in terms of lower yields. We haven't seen a penalty. But, again, it's early days so things may change. If we find a need for lots of nitrogen fertilizer, that would be a killer.

Audience member: A question for Jennifer, following up from what Alan was asking. You said you are taking more of a functional-food approach toward regulatory or safety tests and so on, but you talked about genetically engineering bacteria, so doesn't that raise a lot of flags? Martin, for example, had a 10-year program to try to get it through regulatory fences. Can you comment on that?

Smilowitz: We are not going to genetically engineer any plants or other commodities. We identify the molecular targets in milk and see where else we can find them. For example, human-milk oligosaccharides are also found in bovine milk, which we drink. And they are found in whey streams which are used as a by-product. We are enriching those. In terms of safety and efficacy we are using milk, which is pretty safe, right? We aren't having any issues using this product with neonates.

Audience member: Okay, but how are you enriching them?

Smilowitz: By engineering. With the Hilmar Cheese Company, we are using specially engineered pores to enrich them.

Robert Wager (Vancouver Island University): My question is for Martin. First off, congratulations on fabulous work. It must be very difficult to do biotechnology with all the constraints put on you in Africa. It's tremendous what I saw today. Where are the

field trials of the stacked cassava being done and, secondly, what's your opinion on the news that Kenya this week will finally push forward their biosafety regulations through parliament and how that relates to the difficulties of doing biotech work in most of the countries of Africa?

Fregene: The field trials for stacked products right now are in Puerto Rico, and they are yet to be tested in Nigeria. In Nigeria we still have single-trait events, β-carotene, with iron going to the field. On the question of the legislative and regulatory environment for doing this kind of work, you are right, the whole environment for biotech in Africa is still very premature, very primordial. But Kenya, as a matter of fact, has passed a biosafety law. Right now, they are going through the process of translating that law into a framework of laws that can be implemented. So the Kenyans actually do have a biosafety law. They, South Africa, Egypt and Burkina Faso are about the only ones. The Nigerians are in the process of passing the law, but the toughest part is translating that law into regulations and rules that can actually be used in practice. The Kenyans are now pushing ahead with that. It has taken them more than a year already, but, hopefully, things will improve. The selling point here that is good to mention is that we are looking at these not just as food but also as nutrition products. So when you talk about medicine, people are willing to go the extra mile and do something a little bit more risky than when you are talking about just food. This is also being sold as a nutritional product, and hopefully that will open the doors a little bit wider.

Tom Tomich (University of California-Davis): I'm interested in methods for risk assessment. In her banquet presentation, Dr. McGloughlin effectively put on the table that significant risks result from inaction, from doing nothing. That needs to be considered. But in terms of innovative technologies, there are production risks, which I think we have pretty good methods for, but then there are environmental risks and health risks, with which the methods are much more problematic. And then, getting back to Alan's question, there are also market risks about acceptance. So, my question for each on the panel is, "What do you view as the best practice in integrated risk assessment in your area and, how do you actually frame how those different elements fit together?"

Smilowitz: For integrated risk assessment, we are implementing clinical trials. And we are doing extensive tests with high through-put analyses to make sure we are actually capturing all of the metabolites, to assess which are decreased and which are increased. We are using food as our model. I mentioned earlier that we are using engineering technology to enhance, let's say, oligosaccharides in bovine milk, but it's really through filtration. We're not inserting genes and we're not adding any chemicals; via filtration we are augmenting what is already found in nature. We are not interfering with Mother Nature, and if we can show that with these clinical trials—feeding trials and many are already going on—we don't feel like we are going to have too many constraints. Now the issue is whether consumers will be interested in these products. We're not there yet in terms of market research, but we are working on that.

Edwards: We are increasing natural dietary components of vegetables. Of course we are concerned about and do studies to make sure that we are not increasing them beyond levels that consumers would otherwise get with other diets that are prevalent here or elsewhere in the world. So, there are those kinds of precautions. With respect to the modified oils I talked about, we already have GRAS certification because the oil composition is similar to others in the marketplace. We are already free to use those other oils for the kinds of food-formulation processes that were described, but we work carefully with regulatory and government agents and experts in the field to do the feeding formulations and whatever is necessary to certify health effects.

Fregene: For BioCassava Plus, of the food-related, environmental and trade risks, trade is easiest to deal with. There is almost no trade in cassava between Nigeria and other countries that might turn down GM crops. From the outset we make bioinformatic assessments for potential allergenicity related to the genes we are working with and we also do food toxicity tests—you purify the proteins and you feed them to rats and things like that. We also do environmental assessments. We are working hard to contain all the potential risk, but, as we go along, additional ones will show up. No doubt about that. The good thing is to have an issues-management plan in place to address all of the risks that shows that you have a rational, safe system. That way you build confidence and, hopefully, eliminate apprehension.

Concepcion Mendoza (University of California Cooperative Extension): Martin, yours is a novel approach to solving nutritional problems in developing countries. It's a huge effort with a lot of investment. Have you done any sensory tests for consumer acceptability of these new products, especially using traditional food-preparation methods?

Fregene: That's a very relevant question. As a matter of fact it will be done, but further down the road. We still don't have a lead event selected. We don't have a product that is going out. Our model variety is different from the farmer-preferred variety. Before we jump through that hoop, we will have to have something acceptable to farmers. It's in our product-development master document to do taste, food-processing and preparation tests to make sure that what we are producing will be acceptable, but right now we haven't done it.

Betty Burri (Western Human Nutrition Research Center): Martin, are the high β-carotene varieties of cassava also low in cyanogens?

Fregene: The variety we picked is low in cyanide. But, ordinarily, people process it into *gari*, which gets rid of a lot of the cyanide.

Stanislaus Dundon (California State University): One of the socially desirable aspects of cassava is that the soil doesn't have to be particularly fertile. The crop, as long as it stays in the ground, is like a storehouse. Its short shelf life means that it has to be eaten locally

and that's good because that's where the hungry people are. However, the financial world is interested in a competitive source of cheap starch to ship around the world. I suspect that, all of a sudden, that crappy land may become valuable and local farmers will lose control of it, meaning that the local people will lose control of that food source. Do you have any mechanism for preventing this side effect?

Fregene: I really haven't thought about that, but I can give you my take on land, at least in Kenya and Nigeria. The areas in which we are working in western Kenya and southern Nigeria are heavily populated. The average land size per farmer household is approximately an acre. It's really small. It would be hard for government or an investor from Dubai to buy that kind of land. It would create a social catastrophe; where are you going to move all those people to? So, where we are working, this is of lesser concern. Where you have large tracts of land, less heavily populated, the danger of having that land taken away from them by large investors is there.

Jozef Kokini (University of Illinois): Marlin, I am very impressed with the work that is going on at Monsanto. This is the second time that I have seen this presentation and it is really spectacular. It's wonderful to see that genomics is actually leading to new attributes beyond *Bt* corn. My first question is about the value of these advances to the farmer. I can see, for example, how, in the case of fruits and vegetables, improved quality might lead to value in the marketplace, but I'm just wondering if that would happen also in the case of a commodity like soybean. Will the farmer be able to get a premium, if you will, for improved fatty acid characteristics? And similarly to a previous question, before you launch these in the marketplace are you doing the range of consumer tests and sensory evaluations to determine if their properties are similar to or better than those already available?

Edwards: In terms of the sensory properties of the products from the oil, obviously this is critical. We are starting some of the initial work in house, but a lot of it will be done by food-company partners who have already expressed interest in those ingredients. Clearly, those criteria will have to be satisfied in order for those products to go to market, but our experience so far has been extremely positive. With respect to agronomic properties and benefits to growers—Flavr-Savr was mentioned earlier, and one of the challenges with Flavr-Savr was that it was launched in a product that was completely inadequate for the production region. One of the mantras of our business is that products we launch have equal or superior agronomic and production properties, as well as the benefits from our traits. We don't expect our traits to have enough value to carry them forward if they compromise agricultural productivity and farmer profitability. It's clear that some of these traits will require some channeling in the marketplace in order to get them into product streams where the oils will deliver benefit. There likely will be additional cost for the growers and we recognize that we have to work through the whole value chain to set up an incentive system so that all the players in the process come out equal or advantaged. We've been able to do this in the past and it takes a lot of work, but that is clearly the model to ensure success.