Tie-Up Session

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Ithaca, New York

Panelists:

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Karen Kindle: We will start with an overall question for the panel, then address some pre-submitted questions and then open it up to the audience for general discussion, because I think the conversation has been excellent during the audience Q&A. The thing I want to start with is—it's fun to go to a meeting and hear exciting talks and new ideas, but what is the impact when you go back to your day job? How do we progress from presentations to a call for action? In the areas of technology, regulation and public opinion, what should be the call to action for the participants of the meeting and for NABC? Who wants to start? Don?

Donald Weeks: This technology has potential to influence people's lives in a very positive way. It has the opportunity to impact how we feed the growing population we have across the earth. I see so many opportunities to make modifications to plants that are going to make real differences. I want to get back into the lab and help make that happen. What I'm not going to go back with, with great joy, is the realization that all my efforts up to this point—and maybe for the next few years—have come to naught because people who don't understand the technology, but who want to oppose it for whatever reason, are going to set up serious roadblocks to seeing the technology do good.

Daniel Voytas: We have focused a lot on how the technology can be used to create plants with new traits, and we have compared and contrasted it to state-of-the-art biotechnology. As a technology developer, I think that we can make it even more precise, more controlled, more predictable as to the outcomes of our genetic modifications, to minimize concerns about off-target effects. It's something we should continue to keep our focus on, so that when the public does ask questions we can say exactly what sort of modifications we are making.

Neil Hoffman: I prefaced my talk with some of what I had heard at this meeting. I have made additional contacts, including the kinds of information that Dan mentioned about additional reassurances from the risk point of view, which are always good to know. We have a long stair to climb and we need to go steady and keep pushing. I am glad to have met you people and any information that you have regarding safety may be useful for us in formulating our regulations.

Gregory Jaffe: I think that the take-homes for people in the audience are—and I would pick up on our luncheon speaker, Jeanne Colleluori[1]—transparency and providing information. Lots of great science is going on at universities and in industry, but don't stay in your ivory towers. Make sure that you are transparent about the information. There should be engagement and, especially, communication of science, not just to the public but, as opinion leaders, to the communities that you are in, as well as to the government. Government regulators are not what you think; they don't hear enough in comment periods from scientists—who can provide both technical and useful information—as well as from important stakeholders who need to be heard from.

Drew Kershen: I'm going to say, "I don't know." I don't know where we are headed. I really don't. I'm convinced that the science is sound. I am impressed—not just from this meeting but from other things I do—that the breadth and depth of the science is phenomenal. On the other hand, I am not convinced on my pessimistic days—and this is not necessarily a pessimistic day—but I am not convinced that this will go forward. The issues of public perception and how it is shaped are crucial. We had a very nice talk form Jeanne Colleluori about how Wegmans food stores are trying to navigate a very difficult field. But if the food retailers begin to say that we are not going to use these foods because we think that that is what our customers want, and if we get into additional international trade disputes, such as we are in with China right now, which has resulted in many expensive lawsuits against Syngenta—I'm not trying to favor one side of the other, I'm just trying to be a good reporter—I do not know which way it's going to tip. Someday, we may look back and say, "Why didn't we use this technology?" We've seen that already with Golden Rice, and we let thousands of children go blind and die each year as a result of regulatory obstacles that are basically unnecessary. You could release Golden Rice and let people try it. You may think I'm passionate, but I'm pretty good friends with Ingo Potrykos, one of the developers, and I'm not a quarter as passionate. Truthfully, Potrykos is in agony about

[1]Pages 223–230.

this because he spent his life trying to do something good for people, and he did. Now it's blocked and he's convinced he will die without ever seeing it help a single child. I'm not trying to be negative, I'm just saying I don't know which way it will go. I have my hopes and dreams and I have made a commitment to my own self and to other friends: I'm going to continue to speak and write and say what I think is the truth as best as I know it and stand up for it. If, at the end of the day I lose, I'll say that I tried my best.

Perry Hackett: I feel the same way, but I'm also taking back two messages to myself. One is that when I say you can't educate the public, I'm certain of it after today. I asked Greg Jaffe how he felt about GE foods, and he said, "Well I don't know." Come on! There aren't a hundred people in the world with your background and everything you've been exposed to, and you're not sure? You have patience. No one else has that patience. Not one aspect of GE foods has been brought up, that I know of, by anyone in any context, with animals at least, that offers any possibility—any possibility—of harm if it's not already harmful to the animal. I just don't know of any. And I don't know how you educate against proving negatives. That's what the public wants, but that's impossible. So that's one thing I take away. The second one is a simple question to the regulators: "Is it possible for a small company to get any GE product through?" And the answer is "no." Period. It's "no." It's the time that it takes. It's the expense of going through all the trials. I heard at this meeting that it costs $200 million—that's a maximum cost—to get deregulation of another event by a company that's already well established in the field. And Drew Kershen gave us the number $78 million so far for AquaBounty. Those are unrealistic numbers for people who want to bring some creativity into the world. So, where is it going? Well, you can be negative that it won't get out, or you can imagine that it's going to go underground. We can build essentially any genetically modified animal for about $100,000, and maybe about another $100,000 to show that it's actually healthy. This is leave-no-trace technology. There's nothing to show that if you do this in Brazil, Argentina or Nigeria and say, "Look, I have a new mutation; my cow doesn't have horns and I'll be sending 1,000 straws of semen to various places in order to get this genotype out," there is no way anyone can prove that that is not exactly what happened and the regulatory costs are essentially nil.

Kindle: Well, that is an interesting opinion and we hope that Drew will represent you and will be able to keep you out of prison. Let's go ahead to some maybe less controversial pre-submitted questions. First:

> *The specificity, the precision of gene editing depends on the target sequence and reagent, thus genome editing is not always precise. It's focus is on product. What are appropriate standards for determining whether or not there are off-target effects that affect the safety of the product?*

And second:

> *I agree that our regulatory system does not work well. However, should we be more forthcoming about off-target effects in our research and in these discussions, or does everyone really think they are so minimal we can ignore them without risk?*

Dan, why don't you start with this?

Voytas: As I have said, the technology is powerful and, in fact, off-target effects are rather infrequent. However, I think that we could set very reasonable standards for the types of products that are released. We have pretty good genome sequences for most of the plants and animals we work on. For a fairly modest amount of money we could determine the genome sequence in the plant or animal we are about to release to show that, in fact, the only mutation is the one we actually wanted.

Weeks: I'll second what Dan said. Especially with the cost of sequencing going down very quickly, it's not going to be a major burden to take the event that you want to bring to market, do a complete genome sequencing and show that there are no new mutations in any gene of any significance that you can recognize in the whole genome, and use that as good evidence that there are, likely, no off-target effects. One of the frustrations in science is that you won't get a scientist to say that that something is never going to happen. You can't be honest and say that. You can say that you have looked the best you can and the chances of something negative coming out of what you have done have very little probability. That you can do, and I think we will be able to say that in terms of looking at off-target effects.

Kindle: Thank you. The next question relates to the precision of the process and, in my mind, how much it can be scaled up:

> *Enzymes and transcription factors from different organisms have different efficiencies. Do these technologies allow for closely related enzymes and transcription factors, one or two different amino acids in the active site to be precisely modified, effectively mutagenizing a poor-efficiency enzyme or transcription factor into a more effective one found in other organisms?*

That's the first part, and I have a related question:

> *What is the potential throughput of this technology, especially for enzymes that can be tested only within their native context, and how much optimization of proteins should we anticipate?*

Voytas: With respect to the first question, we can go in and make pretty much any modification we want in any gene we want whether it has a transcription factor or not. That capacity is currently there. As we look towards the future, screening *in vivo* for variations of interest is certainly a possibility. Plant-pathogen interaction is often a receptor-ligand interaction that triggers a response, and so we have that continued war between plant and pathogen. You could imagine screening large numbers of variants *in vivo* with resistance genes that would recognize new ligands produced by various pathogen—a whole new approach jumping into the evolutionary process yourself and engaging in the war between plant and pathogen in a useful way. Those kinds of opportunities will be there as the technology improves and becomes more efficient.

Kindle: Let's move to the area of communicating with the public and public acceptance:

> *How should scientists address the public on the subject of gene-edited crops and livestock?*

And a second, related question:

> *It's clear that many people in this room can be thought leaders within their communities. Are there non-technical thought leaders who might be receptive to technical arguments?*

Could we go to Kim Kardashian or Justin Bieber? We don't want to waste our time talking to people who are never going to be open to the arguments, but having someone who has changed her or his mind or learned something and is willing to be a proponent seems to me an opportunity. I think Greg will be the person to address that.

Jaffe: A lot of people are open to scientific arguments. I didn't mean to leave the impression that they aren't. But, you can't assume that all consumers are going to act rationally or be convinced by scientific arguments. There are lots of opinion leaders and there are lots of nonscientists who will listen and be persuaded by scientific arguments. I think we need to do both. We need to both talk to people about the science and about the evidence that's out there—not dumbing it down but realizing that you may be talking to people of various backgrounds. You also have to understand, and not be frustrated by, people who do not agree with you even if you think that the science is overwhelming; they may base their thinking on nonscientific factors that are important to them, rendering the science irrelevant to them. There's a false sense that, if you keep saying louder and stronger that GMOs are safe, it is going to convince some people. There are lots of rational people and lots of organizations and government people and those who work for NGOs and others who are convinced by scientific argument. I'm often in scientific audiences who think, "If they only understood the science then, obviously, they would be with us." I want people to understand that that's not always the case.

Kindle: Heather Shearer[2] suggested a website that she has found useful. Are there are gaps we should fill, or is there plenty of available information that people can refer to?

Jaffe: There is definitely a lot of consumers or a lot of the public out there with perspectives about information, for example from corporations that may be right or wrong, but they do have that. And they may have specific views about specific corporations. The biotechnology industry has added a new "GMO answers" website thinking it would be the solution for this, that it would provide opportunities to interact more with consumers and answer their questions. That may persuade some people, however a lot of people will see it as a biased source of information and are more likely to be swayed by academics at Cornell and elsewhere. Although Wegmans is a corporation, it's a trusted source for many

[2]Pages 193–199.

consumers. Their responses to GMO-related frequently asked questions are scientifically accurate, understandable to their customer base and written in a folksy way that fits their corporate personality. That's probably not persuasive to 100% of their customers, but it is persuasive to a lot of their customers who visit their website and their stores. I often tell people to look at that because we need more similar communication from credible sources. And academics and universities can be included in those sources.

Voytas: The notion of consumer traits was brought up several times. We don't really have the capacity to market our technology, but with products like acrylamide-reduced potato and allergy-free peanuts—benefits that consumers can directly see—it will bring a link between the consumer and the science.

Kindle: I'll make this the last of the pre-submitted questions and then open the discussion to the audience. This one talks about the harmonization of GM regulations in order to maximize international trade, but while this works for large corporations it may not help small farmers. I think the questioner wants to explore plusses and minuses of having a more harmonized international approach to regulation.

Hoffman: I don't know the answer to that. It's hard enough to harmonize now and, if we change things, I can see that as a real key issue for us. I'm sorry I'm not the right person to answer that.

Jaffe: I caution people on harmonization. In the international arena, a lot of time when you have harmonized regulations, it ends up being a lowest common denominator. While we may all think that that is fine for GM, it might not be for *Salmonella* or for *E. coli* or Ebola or something else that we, as Americans, really want to trust our FDA on and may want them to have stronger standards than some other countries in the world. With that in mind what I do support, and strongly urge, is harmonization of requirements of scientific data and risk-analysis frameworks. To me, that is very important and I think that is something that can be achieved so that the scientific community and governments and others can come together and say, "These are where the potential risks are in a GMO for food safety, and these are the tests that are state-of-the-art and this is the way you do those to cut down on the cost factor." If all countries would harmonize that, then they may still make different decisions and they may have different timelines and different public-participation processes in the formulation of regulations, but they all will be looking at similar data, which for developers and scientists will result in savings in cost and time.

Kershen: Some other ideas on international harmonization—it would be helpful if countries would be willing to allow recognition of decisions of other nations. It would be helpful if you didn't have to go country by country because you have to repeat the data. Part of it is just what Greg said: the data requirements from country to country vary, but even if you had the same data requirements, the question is, "Do you require that they be redone for each country?" Let's say we're talking about growing. Well, our environ-

ment is different from that of Canada and you can carry that into, "Well, our county is different from the next county." How far do you carry that? And so the issue becomes, "How often do you have to repeat these?" It would be very helpful at the international level if we could just simply agree to give some level of recognition to the data in other dossiers done by other nations so that we don't have to constantly do it again and again. And there are, allegedly, mechanisms to do that through the World Trade Organization, but the WTO hasn't really addressed these issues significantly. A lot of the issues that I see in terms of barriers to international trade are actually violations of WTO agreements and obligations. However, that is a very difficult thing one, to prove, and two to enforce, and so international relations are still very much an area in which there are lots of treaties and regulations and laws, but the enforcement side in getting cooperation is still lacking.

Kindle: I would welcome anyone wishing to share what they will take home from NABC 26 and what they will do as a result of what they've heard. Also welcome are questions for our panelists. So, let's open it up now.

Reuben Tayenga (Washington State University): For those of us who are considering using these technologies to modify genes of interest, what are the chances of success at the first try? Secondly, what are the chances of modifying genes closely related to the gene of interest?

Voytas: A lot of people have used the technology successfully. Whether at first try, that's hard to say. Even in my lab, my graduate students and postdocs sometimes don't get it on their first try. Particularly CRISPRs are pretty transparent and easy to understand; protocols are well established and can be followed. With regard to your question about affecting closely related genes, it comes down often to the design of your nuclease. You can get a nuclease that will bind to one particular gene but not to another in the same gene family because of sequence variation and the DNA-binding recognition domains. So that is definitely doable to target one member of the gene family and leave other members unscathed. But it takes a little bit of effort and thought in terms of your nuclease design.

Weeks: On the other hand, you can knock out a complete gene family if they are very homologous, so there is a world of variation there. It's powerful.

Gary Rudgers (Dow AgroSciences): One thought I had on off-target effects and sequencing the entire genome—unfortunately, not only does the public, but also regulatory agencies in some countries, think that one corn-plant genome is identical to the next corn plant and the next corn plant, that there is no variability whatsoever. That's not true in all countries, but I know that it is true in some. So, when we look at off-target effects trying to sequence the genome to show that there is none would be an impossible task because you would then be asked to confirm and justify every single mutation that you identify, which could be in the thousands or even tens of thousands. What I would hope to see is comparison of the off-target effects with these technologies to what occurs naturally and

also to compare them to chemical and radiation mutagenesis. There have been conversations that the off-target effects could be significantly less using these technologies. That is something that does need to be addressed, and I think we need to put it in some sort of context there sooner rather than later, to help clarify that to regulatory agencies. I know that, in Japan, they are very interested in this. The regulatory agencies in Japan are concerned about off-target effects, even though they have been told that the off-target effects would be less than with chemical and radiation mutagenesis in which Japan is probably number 1 or number 2 of the countries that use products developed through radiation and chemical mutagenesis. So, I don't know if there are any thoughts or comments on that, but I know that reports on this topic would be extraordinarily helpful to clarify the off-target effects of these various technologies.

Weeks: I agree with that. I should clarify that I think that anyone who is setting out to do genetic modification with these technologies—who does want to compare genomes—that they start with "a" genome of "a" plant that the sequence is already known so that they can compare to that one plant not every plant out there.

Voytas: Robin Buell and Nathan Butler are here from Michigan State and we have a joint project to make a handful of modified plants from the same mutation in a herbicide-resistance gene using TALENs, CRISPR/Cas, EMS mutagenesis and transgenesis, introducing the gene, and then sequencing the genomes of those handful with individual events to get an assessment of the amount of variation you see. We and others are trying to gather that sort of data, which will be useful.

Patricia Polowick (National Research Council of Canada): Two things—one comment and one question, totally unrelated. The first comment is, I do think it is possible to move through the regulatory system more cheaply than what has been mentioned, with a small company. We've heard a lot about the Arctic apple and I know that's a very small company because two technicians have been embedded in my lab for a number of years. I know of only five employees in the company, including the owner, who is supported by other orchard growers around him and they've gone through the whole procedure one step at a time, outsourcing, for a lot less money than has been suggested. My question: I've caught the tail end of a series of commentaries—I don't remember the website—suggesting that some of the bigger companies, like Monsanto, offer money to anybody who wants to do research to prove that there are dangers to GMOs. Would there be any merit in that or would it attract only scientists already accepting of the science?

Kimble: Who would like to take that?

Weeks: I think that's a brand new idea to most of us. I've thought a lot about this. If I were one of those evil Saturday-morning-cartoon scientists, how would I modify a plant—and I guess this would pertain also to animals, but plants are my business—how would I modify that to do harm? And, boy! That's a tough nut to crack. I couldn't come up with what I

thought would be a significant approach to that. That realization tells me that this effort would probably not succeed. I can't say it wouldn't, but it's hard to prove a negative.

Voytas: Scientists are already contributing to that thought—Gilles-Éric Séralini, for example. You are saying that a company with deep pockets is offering money to a scientific group to show that GMOs are dangerous. We consider Séralini's experiment as bad science, so I'm wondering about the feasibility of this. Would the company be paying for bad science? In a Greenpeace-supported study, some Russian woman found that GM diets created harm in an animal-feeding study. There are several examples of that. How would you separate the bad scientists, the people who have an agenda and are receiving money? Now would they be getting it from industry to do the same sort of studies?

Polowick: I look at it more as "put up or shut up."

Voytas: There's a fairly large literature of poorly done studies that don't stand up to the weight of evidence, and now you're asking industry to feed those kinds of efforts. I think you would find takers, is what I'm saying.

Kindle: Let's move on to the next question.

Adam Bogdanove (Cornell University): I want to share some comments related to a couple of questions back about off-targeting. I advocate caution in generalizing about the precision of the technologies, because inherent to the technologies is selection of the target. And, depending on the target, your off-targeting will vary, either as a function of the sequence itself and how commonly related sequences occur in the genome or as a function of the reagent you are using, particularly in the case of TALENS in which a TALEN designed for that particular target may have greater or lesser specificity as a function of its RVD composition. The other part of that relates to Reuben Tayenga's question. Gene redundancy is a big challenge for gene-functional analysis. If you want to knock out many members of a family, I think you can do this, in some cases, with a single reagent. If, for one thing, as Dan Voytas says, you can find a conserved sequence that that reagent will target, but also—I just wanted to pitch this idea again—that with this sort of tunable specificity of TAL effectors where they can be engineered, we have examples from nature in which they have more or less stringent specificity, we can capture that and exploit that for engineering to get sort of a specificity profile with just the right degree of lax specificity to capture a series of paralogs that may have polymorphisms across. This off-targeting is something we seek to avoid in genome editing. But I think it's something we might be able to exploit for cases like this.

Hackett: I'd like to make a comment about off-targeting. I breezed over it in my presentation, but we can use human beings as an example, at least for mammals, in terms of genomic variation, because close to 10,000 human beings have been done now. There have been several triads—mom, dad and afflicted child—and there have even been some

quads done, which means close siblings or even twins, to try and narrow down the genetic basis of disease. Right from the get-go, we know that we each have about 6 million single-nucleotide polymorphisms. There are a hundred active retrotransposable elements in each of our cells. Most of them aren't actually activated and hopping around, but many of them do and the more we look the more we find. Generally, we just disregard those changes. We have any number of larger changes. Some of us may be afflicted with triplet nucleotide diseases and the like. We know that over 200 genes are inactivated in each one of us on average and 20 to 50 of those are, indeed, disease-related genes. So there is a context for off-targeting, but we have to appreciate that nature can take a lot of variability in genomes and I think that, in this room, all of us are doing just fine.

Abel Ponce de León (University of Minnesota): In the last 36 hours I have heard many, many interesting opinions, and I thank all the speakers for what they have presented and the audience for what they have contributed. Depending on where we stand, each one of us is trying to look for a response, a yes-or-no kind of situation. And I think this is not the case because there are very many positions and variations in between, and many very different opinions some of which we are witnessing right now. This conference is an attempt to assemble the available information in one place to try to see where we go from here into the future. I guess everybody wants the best outcome, never mind which position you have. The public, the consumers, the industry, the researchers—everyone—the goal is the same. But the art of negotiation to get to that point is what we need to master. I wonder what should be the objective of this conference. Should we start defining a path to take—because we are all here in some way representing different sectors—that will make this a successful outcome. And if it is possible to start working on definitions of what to do where we, the different sectors, become more comfortable and at least allow us to go 10 or 20 steps forward, without reaching the ultimate goal but at least moving in that direction. Can any of you address that?

Weeks: Certainly, I agree that this conference has been every informative. We have seen different sides of the issues from basic science to regulatory aspects to public acceptance or non-acceptance of this technology. Finding a way forward is terrifically complex though, because there are many aspects. Many people in science, many people in the regulatory agencies, and certainly many different voices out there in the public exist, and how you address all of those is a major challenge. But, I couldn't agree more with Jeff Wolt's comment that at least we in the science community have to be available to speak about these issues and tell things as they are, what the capabilities of the technologies are, and what these technological capabilities are not. If a pathway can be laid out that people can agree to, many will rally behind it.

Voytas: Many of us have gone to the USDA and asked, "Is our product regulated or not?" That is a great first step because it gives some definitive clarity to the modifications we have made and whether or not we can start to deliver products. I worry about coming back to colleagues again and again and saying the same things, but at least that is something tangible we can do and move forward.

Audience Member: Recently it was suggested that genome-editing technologies facilitate the gene-drive process which could lead to species extinction—elimination of mosquitoes, for example. In a letter to *Science*, an Israeli scientist suggested that gene-editing technology should not be made public because it could be useful to terrorists. He even equated it to the atomic bomb, which it certainly is not. What are your opinions on how to eliminate potential gene-drive issues.

Hackett: I made a prediction a month ago that, two years from now, that's all anybody will be talking about—how scientists will use gene drives to propel certain species to extinction, and that everything we are talking about today will be old-hat history and totally dead. In other words, I think it will terrify people what the power of homing nucleases can be when used for purposes of driving species to extinction. It's one step to say that you are going to have a gene drive in a mosquito that might bite a cow that is going to be eaten by a person for somebody to claim that it will drive human beings to extinction.

Ralph Hardy (North American Agricultural Biotechnology Council): I want to follow up on Abel's comment. We have here a strong representation of the scientific community. A contribution that could be made from this meeting is a definition of DNA editing. We need to define what we are talking about before we can start to sequence what the steps are down the road. So, I would appreciate it if we can have comments on what you think the definition should be. We at NABC will take your comments and synthesize an overall comment, and then send everyone a copy of that. If you cannot live with it, and I use that proviso, if you cannot live with the way it is, we want to hear back from you so that we can find something that you can support. If we can develop a statement like that from this meeting I think that it will be useful to a number of entities as we go forward. I would appreciate inputs on a definition for DNA editing.

Voytas: One reason for a definition is to "anchor" regulation and policy decisions. If you break or lose a DNA sequence—that form of editing—we have some regulatory guidance from the USDA that this is not a regulated article. But when you talk about replacement, it becomes more tricky. How many nucleotides over what span of DNA is it an edit versus a transgene? Is it 30 nucleotides over how many base pairs? It seems like you have to make some sort of arbitrary decision to guide you in then evaluating the plants and the modifications in them. I can edit a soybean into a corn plant. That's a significant amount of change that I am going to make to that soybean genome. I hate setting arbitrary decisions because I can also make 30 nucleotide changes in a kilobase, and I could create a very immunogenic protein that is going to cause allergies. You still have to have a case-by-case basis, but you need, I think, some framework for guidelines. I'm not comfortable saying what number of nucleotides for what span of DNA it would be, but I think maybe something like that is needed.

Hoffman: From a regulatory point of view, we are moving to a place where we are not concerned with what techniques are being used and whether one base is changed or a

million. We are interested in what the phenotype is going to be. Maybe I didn't emphasize this. If we change our regulations, we are going to be changing the regulatory trigger and this notion of what we are saying now *vis-à-vis* "Am I regulated?" may not hold true with a revised regulation. I'm not sure that I emphasized that enough. We are really interested in what the phenotypes of these organisms are, as opposed to what processes are being used. And that's the message I was hearing from many of you in the audience, that that is what's important.

Jaffe: Ralph, I can't give you specifics of the definition. I think it would be good to have a definition, but I also think that it's not the be all and end all, because, from a policy or regulatory or legal point of view, as we saw from Peter Whitfield[3], there's a bunch of definitions out there that may have all kinds of unintended consequences as technology changes. To me, the more important thing is flexibility. Flexibility to learn and then to adjust as needs be and as new technologies come along. It's important to put down what things are today, but you have to have the flexibility to put things in and take things out and move things around as we learn more and technologies change. Otherwise, we may waste a lot of effort if we are so set on one definition that it takes a long time to come up with a new definition. The better thing in the policy context is to have flexibility.

Hardy: This dialog is great. Let me put the definition off to the side. I am beginning to get a synthesis from you of what is important in the long term. The more comments we get to provide a good synthesis, the more productive this conference will be.

Weeks: If I may make a comment as a scientist involved in this technology—I don't want to put words in your mouth at all, Neil (Hoffman)—but if there was a paradigm shift in going from process to product, what a terrific event that would be!

William Haun (Cellectis Plant Sciences): When Jeanne Colleluori[4] was talking about labeling, the comparison she made was GMO to high-fat and high-salt food. She didn't compare non-GM to high fat and high salt, and. when telling us about her proactive task force, she compared GMOs to pink slime—not directly, but that was her train of thought. Even for the person we brought in to speak to a group that is very "pro-everything you've been talking about today," it was natural for her to make the comparisons of GM to high salt and high fat and GM to pink slime. I think that is interesting.

Kindle: I'd like also to return to consideration of semantics with another presubmitted question:

> *Should we help smooth the way with the public by choosing our terminology for gene editing to be more consumer friendly?*

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[3]Pages 217–222.
[4]Pages 223–233.

You could expand that to other forms of GM-type technologies. There's an opportunity for scientists to get training in talking to lay audiences because it's difficult to take jargon out of our vocabulary. There are some excellent books about how to put together sticky messages and cursive knowledge.

Jaffe: It's important to make things accessible to the public; what you choose to call something can have significant impact. When I got out of law school, I considered myself an environmental lawyer and worked for eleven years with the government on pollution mitigation. I worked against corporate lawyers and people who were defending corporations who also considered themselves environmental lawyers. I didn't consider them environmental lawyers, but they tried to capture that phrase and call it their own. The language you use and what language gets captured in the debate is vital. In the United States I use the term "genetically engineered crops," which I think is more scientifically accurate. When I go to Vietnam or Kenya, for example, I use "GMO" because that is what they know and that is all that they know. But, in my view, that is not technically correct and has negative connotations and the people who initiated that term in some ways have won. They've started the discussion at a level that I think is loaded in some ways. I am forced to use "GMO" because if I say the other thing they don't know what I am talking about. When we move forward with these gene-editing techniques, what we call them and the language we use around them will be critically important.

Michael Kahn (Washington State University): There's another aspect to the problem that you are talking about, something I call "entanglement." When you start talking about GMOs and then you put that together with high-fructose corn syrup, for example, people will say, "Well, GMO high-fructose corn syrup is bad for you, therefore GMO is bad for you." And the science of GMO came from Monsanto, and that is a bad word. Perry did a very nice job of breaking apart a number of different arguments that are used in this area. What you find when you move into the public domain is that people slip from one of those topics to another very, very quickly. So that, if you are defending GMOs, you may find yourself defending high-fructose corn syrup when that wasn't your intent, or defending Monsanto's right to screw farmers when that wasn't your intent. One of the things that we have to learn to do is to break out some of these arguments and try to deal with them as unconnected, unentangled arguments. In most cases they can be dealt with one by one, but, when you are talking to the general public, they don't see these segments—it's all one picture, and I don't know how to deal with that. How does one keep control of the topic?

Jaffe: Your example could be another one of language. The high-fructose corn-syrup industry is now petitioning to call it "corn sugar" specifically for the reason that people are beginning to think that high-fructose corn syrup sounds artificial. I come back to the idea that things need to be put into context, and the public's lack of knowledge of agriculture and of science around agriculture is a real problem. We are always going to have trouble communicating about genetic engineered crops, for example, when people just don't

understand the breadth of what goes on in agriculture and what it takes to bring food to the table. To me, the most important thing is context. I don't have any good answers, but in CSPI's newsletter we deal with highly scientific topics and summarize the latest research on diet, cancer, *et cetera*. The people who write in my office do a really good job of taking highly scientific, technical peer-reviewed articles and put them in language that people can understand without dumbing it down. Our subscribers can understand the information and apply it to their diets. We need to have communicators who have those gifts to work with people like you and me.

Kindle: In addition to not understanding agriculture, many people do not understand how science works. And I'm not talking about the scientific method, I'm talking about the fact that if a scientist expresses doubt, it means something very different to a lay person than to someone who understands how the system works. Recently I read an interview with a plant molecular biologist in Florida and almost the entire exchange was about how science works. As scientists, we assume that everybody understands that, and yet they don't. They don't know what peer review is and how you prove or disprove a hypothesis. Things like that. So, there is an opportunity for that kind of communication as well.

Margaret Smith (Cornell University): A couple of comments about language, I would remind us all that "GMO"—also my least favorite term for genetic engineering—was coined by those who were trying to think of a term that sounded more friendly than "genetic engineering." It was actually coined by the people who supported that technology in order to make it sound softer and less like "nasty scientist in the lab" than genetic engineering. It's important to be thoughtful about your terminology, and you have to realize that it may be co-opted. The other thing I thought was interesting is the way we talk about this. One of the questioners talked about us being an audience who are pro-GM. What we should be is an audience who are interested in the pros and cons of particular phenotypes rather than being pro a tool. So, we also need to be careful how we think about ourselves. And, further to one of Greg's comments, I think we need a jingle and one possibility is "apply it to your diet."

Dana Carroll (University of Utah): Perry, I think it's okay if I tell people what Scott Fahrenkrug calls introgressing a natural trait into a different breed. He refers to it as molecular breeding, and I don't know if "molecular" will kick it out of camp, but it's another attempt to modify the terminology to separate what he has been trying to do at Recombinetics. I have a couple of comments, trying to make useful suggestions. People talk about Frankenfoods and Peter Whitfield[5] showed a picture of a banana with a fish head; so, I think that, in promoting what the technology can do, we need more pictures. It's a vocabulary that the public in general can understand better than arguments that are based on producing obligate heterodimer modifications with a cleavage domain with zinc-finger nucleases (which actually is a really good thing to do; it improves safety). So,

[5]Pages 217–222

one idea is to get more images that can be used in the argument. The other idea is to enlist local outlets to make the case in a way that is more easily digested. One example would be—I don't know whether this sort of thing has happened—where a small company has sprung up, perhaps a newspaper or TV or radio station could be enlisted to do a feature on the company from the perspective that it is locally advantageous economically. It's doing something that is positive, like an apple that won't brown. It would direct the conversation away from the international level and down to a local level and influence neighbors and friends with simple, locally understandable conversations, and lots of positive images may help.

Greg Gocal (Cibus): I'd like to extend that comment regarding influence locally and broadly. At Cibus we've had an internship program for forever. Over years we've had 30 interns who have worked through me, and even if they decide not to stay in science ultimately, I think it's a good way—just like talking to your neighbor—for them to acquire experience and knowledge about the sorts of things that we work on on a daily basis and the advantages of them. The more interns and the more academics talking to their classes about variation and how we can move that around and the new technologies that are beneficial, the more likely we are going to have broader influence. I can't remember where I heard this, but in our lifetime we probably meet 1,000 people or 10,000 people—in that range—and if we deliver the same message to each of those 1,000 or 10,000 people, we have the opportunity to share the message around the whole globe. And so we, individually, have to take responsibility for choosing the right words to deliver our message, and I agree that that is very important, and we have to tell people clearly why we are trying to do this in terms of food and the local population and the potential advantages. I will leave it there. This has been a great meeting and we have a collective challenge that we have to address.