Keynote Presentations

Q&A

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Daniel Voytas: A question for Dana. We now have at our fingertips all these DNA-breaking reagents, and you talked about ways to direct the outcomes of repair—homologous recombination, non-homologous end-joining—so, in the future do you think that we will be able to control the DNA-repair machinery, both in terms of achieving higher efficiencies and very predictably the outcomes of the repair.

Dana Carroll: Yes… I'm working on it. Quite a number of people are working on trying to improve the efficiency of homologous recombination, which, for a lot of us, is lagging. There is a lot of different approaches, and I don't know if it will come through adding components that will enhance homologous recombination, or whether it will come through knocking down and joining; maybe there's an approach that we haven't anticipated.

Robert Millman (MPM Capital): Dr. Voytas, in your expression system, did you use a selectable marker?

Voytas: In my potato example, no selectable marker was used. We knew the framework of the technology and expected efficiencies, so we treated the cells and began screening to regenerate plants.

Karen Kindle (Boyce Thompson Institute): Do the invertase mutations have any developmental, phenotypic or flavor effects?

Voytas: That's the next question. We have just generated the products and we hope, with the USDA's approval, to go to the field to fully evaluate the trait.

Patrick Di Bello (University of Arkansas): Has the FDA given you any indication of how they will regulate the potatoes?

Voytas: No. The EPA must also consider environmental impact.

Vibha Srivastava (University of Arkansas): Regarding the efficiency of gene targeting, you observe 5 percent in potato and 7 percent in tobacco, which are easily transformed, but what do you expect in species that are more difficult to transform?

Voytas: For many species, getting the nuclease and the donor molecule into the cell remains a challenge. The potatoes were easy because almost every cell was transformed—in excess of 80 percent of our cells took up the reagents, so many of the plants that we regenerated had the target modifications. This will continue to be a challenge. You might expect 10 percent of the cells that take up the reagents will undergo the modification you are interested in. You have to identify the cells that took up the reagent, and, among those identify those that have undergone the gene replacement.

Yinong Yan (Pennsylvania State University): I agree with Dr. Hackett that we should focus on the product, not the process. Even though *Agrobacterium* is a plant pest, regulation of *Agrobacterium* as a vector should be abolished.

Voytas: Opinions rendered so far say that if the product does not have the pathogenic sequences, it should not be regulated.

Adam Bogdanove (Cornell University): What do you think is more important: educating consumers about the technology or putting forth products that have a clear consumer benefit?

Hackett: Regarding educating the general public, I don't think you can do it. It's hard enough—when I teach undergraduates in genomics—to get them to pay attention to what I am talking about, even with the threat of tests. What I am finding—because I make maximum use of clickers in the classroom and interrogating the students constantly on where they're at—is that over the past 5 years, and it has just been five years, two obvious changes have been occurring, each of which is a sea-change equivalent to the acceptance of gay marriage in America. Number one, of incoming freshmen, only 2 percent believe that they *don't* eat GMO food; ninety-eight percent think either they are, or they might

be, eating GMO foods, and it doesn't concern them in the slightest. Secondly, most of them feel that regulatory policies fail to take advantage of recent developments, but they also feel that regulatory agencies can be trusted to save them. These numbers and trends result from questions to the students before they receive any instruction, in the first hour of class.

Voytas: To educate the public presupposes that they understand the subtleties of this highly sophisticated technology. As an analogy, when I have dinner with my mother and say, "Hey Mom, I've whipped up a potato that is resistant to chlorsulfuron." she is likely to respond, "That's fine, but God already made a perfectly nice potato that I prefer to eat." But, if I say, "Today I whipped up a potato that has less neurotoxin when fried," she might be more predisposed to it. She doesn't have to understand the subtleties of the science and technology, but she can grasp when something is more healthy. This is the level of approach appropriate for most of the population.

Hackett: In Brazil, you are allowed to eat transgenic this, that, and the other, and labels on the foods have a small yellow triangle that shows a capital "T." The transgenic products sit on the shelf side-by-side with non-transgenic counterparts, and the only difference between them is cost. It's akin to decisions on whether to eat organic or natural produce, for which my students don't really have a feeling for the difference. I trust the Brazilian government that the items on the shelf with the "T" are safe, for the most part—like we trust "non-organic" to be safe, although we may buy organic.

William Haun (Cellectis Plant Sciences): Perry, one of your slides indicated that one founding reason why the system is broken is that the process is regulated, not the product. In Canada, they regulate the plant product rather than the process; regulation is triggered if the trait is novel. Does that system apply to animals also, and, if so, is it at least a step in the right direction?

Hackett: At the *Second International Workshop for Regulation of Animal Biotechnology* in Brazil in August, 2014, a Canadian regulator said that the US policies on transgenic crops are "an utter disaster," and I suggested that, in fact, they are an outstanding example of success. So, we couldn't have been further apart in our views. He didn't like the clumsiness of the statutes, whereas I was looking at the outcome that for 20 years more products in more countries with more acreages are being devoted to transgenic crops, especially so now that the greatest percentage increases are occurring in developing countries where small-scale farmers have the most to gain. In the United States, it is encouraging to see that gene-editing of plants is being suggested as not requiring regulatory oversight. However, that concept remains under consideration *vis-à-vis* transgenic animals. The US agency that regulates animals has not released a single transgenic animal in a quarter-century; they spend so much time trying to expand their control without thinking about revising statutes to bring them more into line with twentieth-century technology.

Greg Martin (Boyce Thompson Institute): Availability of these new methods raises the question of how many interesting target genes in plants and animal do we know enough about to be in a position to start editing them?

Hackett: This technology is equivalent to high-end computing. When IBM first came out with its large computers, the chairman stated that there was need for five of them. Now, everyone of us has a laptop, each of which greatly surpasses those "large" computers in capability. I think that the possibilities of design changes in animals and plants are beyond the imagination of anyone in this room.

Voytas: I second that. Thinking back to my PhD work—I spent five years sequencing 30 kB, whereas it can be done in a millisecond with current technology. And sequencing the human genome was beyond imagination. We are talking about one or two genes being modified, whereas—in line with Perry's comments—in a few years we may be able to make many dozens of nucleotide changes simultaneously.

Karen Kindle (Boyce Thompson Institute): How do intellectual property issues affect you as academics who may wish to see your products in the public domain? Any suggestions for researchers, particularly those in small companies?

Voytas: Those in the genome-engineering community have been very good about making reagents accessible to help address basic biological questions. If a product arises from a targeted modification, that's when intellectual property has to be taken into consideration. A handful of companies have pieces of applicable IP that may have to be accessed for commercialization. Good news, in terms of getting the technology more broadly accepted, is that we have multiple competing platforms, which, basically, drives down the price. If it is too expensive to use a TALEN to modify a tomato, then a CRISPR approach may be a valid alternative.

Abel Ponce de León: Where genomic introgression has been achieved, the intellectual property is basically on the animal or plant *per se*, not necessarily on the knowledge. Have any of your companies addressed this already, and where are they in the process?

Hackett: We have filed patents on several of the animals, but I would like to go to the bigger aspect. It's unbelievably expensive to get taxpayer investments in basic research back to the taxpayers. I started two companies, and it cost me probably a total of $180,000. I'm way in the hole right now, but, hopefully, something may come out. To get any of this stuff out, whether it's *Sleeping Beauty* transposons with chimeric antigen receptors to treat cancer or to get some of these animals out to developing-country farmers who need them, takes an incredible about of money. Investors are not going to give anybody any money to get this technology out to the people who paid for its development in the first place, unless there is IP to protect the rest of the development into a product. Actually the University of Minnesota holds up the dispersion of the reagents that we have. They have

something called a materials transfer agreement, which I hate. I used to share what I had until they put a stop to it because they want everything to run through their hands.

Brent Woodward (Cooperative Resources International): Are you willing to tell us more about the regulatory minefield faced by Recombinetics?

Hackett: First of all, we are completely open. A request was put out by INAD[1] on whether or not Recombinetics and other companies were planning on using gene editing with the idea that the FDA would be able to have a certain amount of discretion to not demand field trials and the like, that would be way too expensive for a small company to afford. Such a letter was sent, and retracted a few days later after a meeting with regulators in the context of another meeting at which it was realized that this meant that Recombinetics was recognizing the legality of the FDA's position, that gene editing was, actually, under their purview. It is our opinion that, in fact, because this is no different from any natural mutation—it doesn't leave any footprint, so to speak, it's not transgenic DNA in the slightest any more—that it really doesn't have anything to do with better regulations. And so, the lawyers actually advised us to retract the letter.

Steve Pueppke (Michigan State University): Is any other country regulating more effectively and doing a better job?

Hackett: Zuoyen Zhu, who was the first scientist to genetically engineer a fish for food, in Wuhan, China—growth-enhanced carp—spent a Sabbatical in my lab and gave a talk in 1987, in which he said that the fish would be released to the Chinese public in 1995, approximately, when adequate stocks would be available. A scientist in our group, Anne Kapuscinski, asked when trials would be completed to determine safety; he replied, 1995. In fact, none of these fish have been released, although China needs fish. But they have deferred to the United States, as have other regulators in other countries. That's the problem—people are waiting for the United States to do it the right way, thinking that we have the most expertise.

Audience Member: Reference has been made to engineering with TALENs and CRISPERs. Will they become part of bioengineering modules that will be used in synthetic biology or do you see them as distinct approaches?

Voytas: If you think of synthetic biology in terms of constructing new organisms to produce products of value, then certainly these TALENs and CRISPERs are enabling tools.

Alan Collmer (Cornell University): Like many other land-grant universities, Cornell has sincerely expressed aims such as "knowledge for the public purpose." I am wondering if

[1]Investigational New Animal Drug for the FDA's Center for Veterinary Medicine (CVM).

the land-grant university system could be a particularly useful voice for guiding us towards more rational regulations and also IP policies that are designed to benefit the public.

Voytas: If you take as a precedent the opinions that have been rendered by the USDA on these technologies, I can see going to horticulture departments and saying, "Do you want to change the color of your petunias?" or "Do you want to knock out a few genes to get rid of anti-nutritionals," then "Here is the technology, here's how to do it, go ahead." If the regulatory barrier is broken down, there is no cost to deploying the technology at land-grant institutions for practical purposes. Clarity is still tentative; only a few opinion letters have been published, but if they reflect the eventual trend, with clearer guidelines the technology will be ready to be deployed.

Ponce de León: Let me add something to that. The majority of the members in the North American Agricultural Biotechnology Council are land-grant universities, and through the Council we are trying to bring to the fore conversations involving various stakeholders with interest in making progress with these technologies, including discussing of pros and cons. We have to acknowledge as scientists that the regulations have political components and regulators have to accommodate both scientific and politic considerations. Through our discussions, we hope that by the end of the conference we will develop novel ideas to propose alternative solutions to manage the conflict and allow us to move forward.

Ralph Hardy (North American Agricultural Biotechnology Council): And returning to the regulatory area, the mistake that was made in the United States in terms of regulations, back in the 1980s, was to elect to use existing legislation, This was probably good in the short term, but it was disastrous in the long term. We've heard about the Canadian situation, where they regulate the product rather than the process, and Helen Shearer will address this later[2]. NABC's 2013 conference focused on the fruit and vegetable area where there are very few genetically modified crops. One problem is small market share, which deters interest on the part of large companies and the other problem is regulatory. Recently, NABC issued a brief white paper suggesting ways of facilitating the commercialization of genetically engineered fruits and vegetables[3]. Also, the National Research Council has begun a new study on oversight and regulation of genically engineered crops. My experience is that our NABC reports are helpful, but those from the NRC carry more weight on the Washington scene than most other sources of information. We have a unique opportunity to provide that NRC committee with our guidance on how to improve the regulatory system, which we should keep in mind during the *Tie-Up Session* discussion at the end of the conference.

[2]Pages 193–199.
[3]http://nabc.cals.cornell.edu/Publications/WhitePapers/SpecialtyCrops.pdf.